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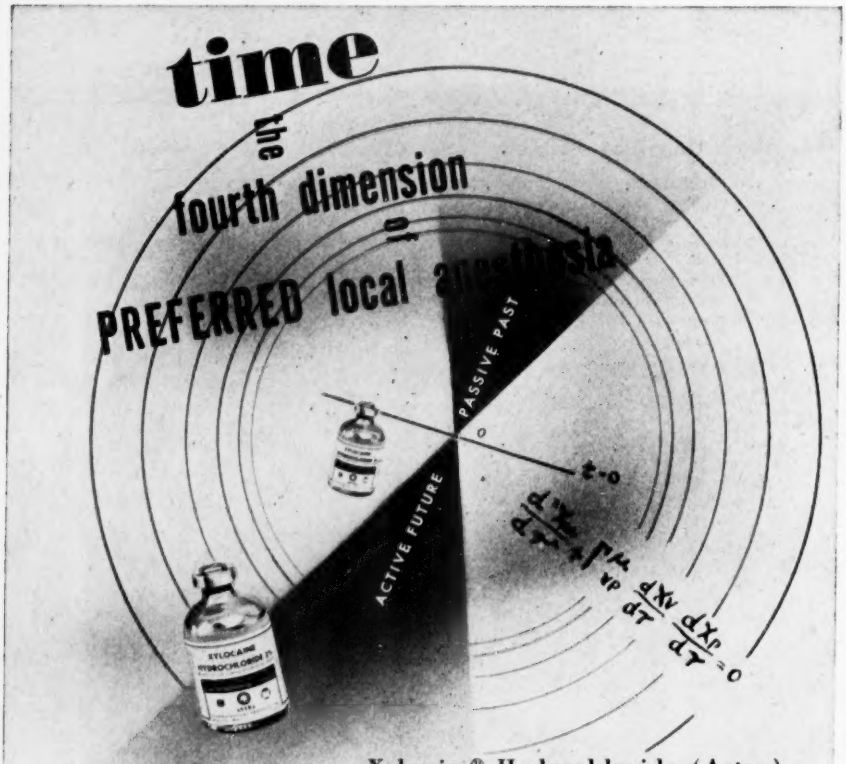

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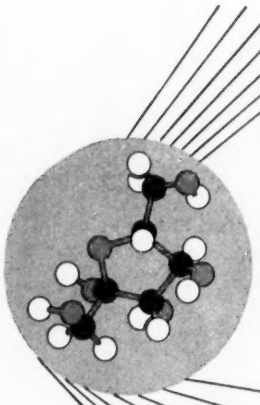

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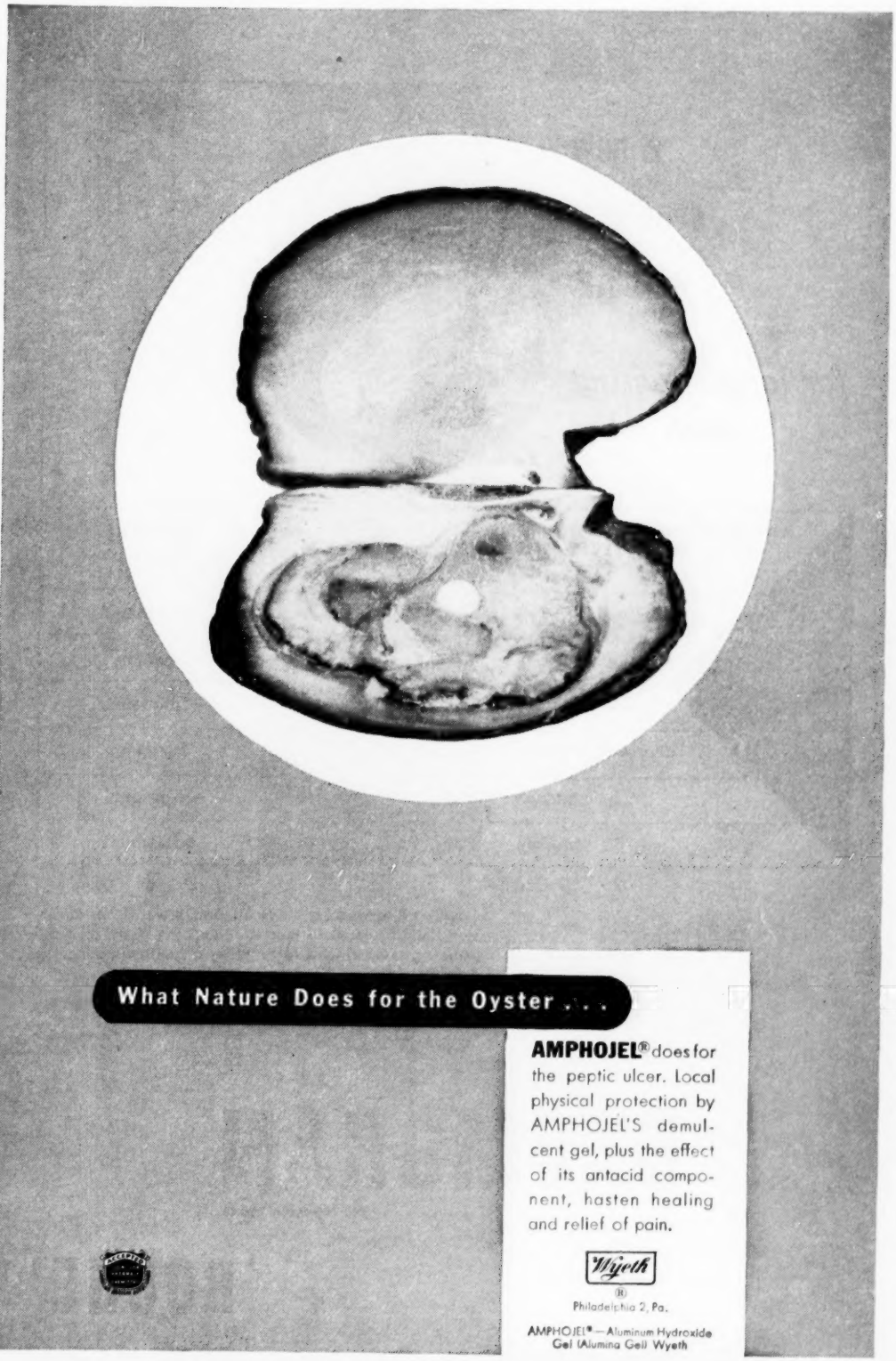
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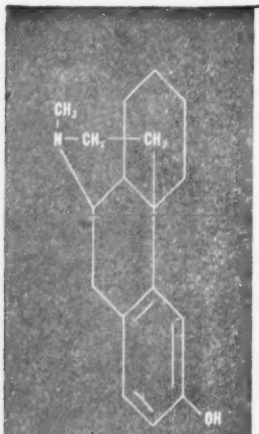

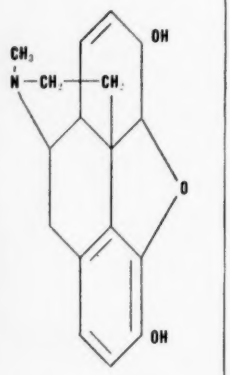

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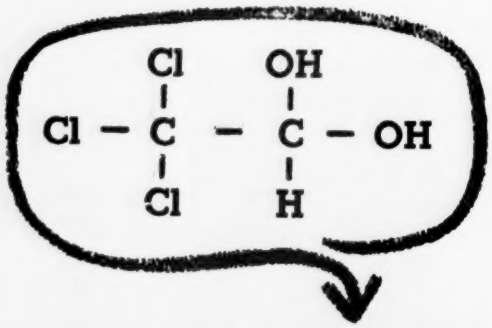

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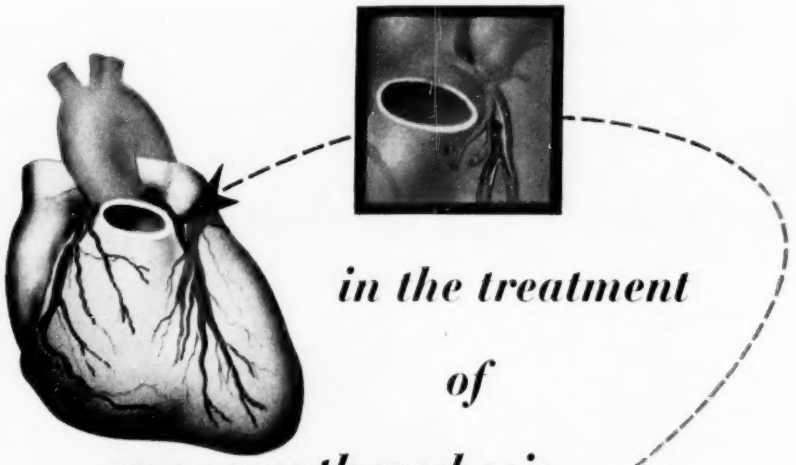

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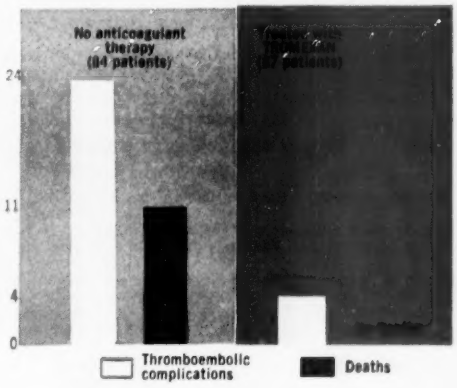

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"CONTINUOUS" VS. "DISCONTINUOUS" THERAPY WITH PENICILLIN*

The Effect of the Interval between Injections on Therapeutic Efficacy

HARRY EAGLE, M.D.,† RALPH FLEISCHMAN,‡ AND MINA LEVY, A.B.§

BETHESDA, MARYLAND

THERE is a considerable body of experimental evidence that the therapeutic action of penicillin rests in large part on its direct bactericidal action, and that the factor that primarily determines its therapeutic efficacy is the total time for which the drug remains at effective levels at the focus of infection.[1-4] Thus, the number of streptococci or pneumococci surviving in an intramuscular focus in mice after an injection of aqueous sodium penicillin G was found to decrease rapidly only so long as the penicillin remained at effective levels.[3, 4] Extremely large doses, providing concentrations greatly in excess of the effective level, were initially no more rapidly bactericidal than much lower dosages; the difference lay merely in the time for which that bactericidal effect continued. In the treatment of experimental infections, — whether syphilitic infection of rabbits, pneumococcal infection of mice, or streptococcal infections in mice and rabbits, — the curative dose of sodium penicillin G (CD_{50}) varied as much as one-hundredfold and more, depending on the schedule of administration.[2, 5] However, the aggregate "penicillin time" required to cure a given infection (that is, the total time for which penicillin had to be provided at effective levels) was largely independent of the method of administration, provided the penicillin-free interval between injections had not been so prolonged as to permit the interim remultiplication of the surviving bacteria.[2] Under the latter circumstances a large number of animals died that would otherwise have been cured, and the harmful effect of remultiplication could be counteracted only by larger doses of penicillin and a longer aggregate "penicillin time."[2]

It is, however, not necessary that effective levels of penicillin be continuously maintained to effect cure. Although the rapid bactericidal action stops as soon as the concentration falls below the effective level, the surviving bacteria do not immediately resume multiplication. In the treated animal,[2-4] as in the test tube,[6-8] organisms that have been exposed to lethal concentrations of penicillin have been so damaged by their exposure that many hours may elapse before they recover sufficiently to resume multiplication. Thereafter, the course of the infection will vary according to the degree of immunity in the test animal. In normal animals, the defense mechanisms of the host may be so ineffective that even minute numbers of bacteria surviving the action of the drug may recover and resume multiplication to cause a fatal infection. In partially immune mice, however, a dose of penicillin that is inadequate for the cure of normal animals may suffice to reduce the number of bacteria to a level within the compass of the host's defense mechanisms.[9] In man, also, it has been clearly established that cure can be achieved by schedules of treatment in which penicillin is given so infrequently that for a large portion of the treatment period there is no demonstrable penicillin in the blood. The fact that such discontinuous penicillin therapy can be effective does not, however, prove it to be the most desirable form of treatment. The possibility clearly remains that bacteria were being rapidly killed only while penicillin was being provided in effective concentrations, whereas in the penicillin-free intervals the infection was in a relatively static phase during which the organisms were recovering from the toxic effects of the drug, and were being disposed of only slowly, if at all, by the host's defenses. Under such circumstances, the most rapidly effective form of treatment would be one that provided penicillin continuously in excess of the effective level, so that both the drug and the host's defenses were continuously operative.

The present paper represents a re-examination of the time-dosage relation in an infection with Group A streptococci in normal, nonimmune mice. The animals were treated with sodium penicillin G by a number of treatment schedules designed to test the

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§Bacteriologist, Section on Experimental Therapeutics, Laboratory of Infectious Diseases, National Microbiological Institute, National Institutes of Health, Public Health Service, Federal Security Agency.

relative efficacy of continuous and discontinuous therapy. The data here reported are consistent with the thesis that the most rapidly effective schedule of penicillin administration is one that continuously provides the maximally effective concentration against a particular organism at the focus of infection; the primary determinant of therapeutic activity is the time for which the drug remains at effective concentrations at the focus of infection; a penicillin-free interval between injections prolongs the total duration of treatment necessary for cure and, if that interval is so long as to permit the interim remultiplication of surviving bacteria, larger amounts of treatment and a longer penicillin-time are required to effect cure than would otherwise have been necessary.

TABLE 1. *Effect of the Schedule of Administration on the Therapeutic Efficacy of Aqueous Penicillin in an Infection with Group A Streptococci in White Mice.**

Interval between Injections	Curative Dose per Injection (CD_{50} and Standard Error)†							
	Mice receiving 1 injection	Mice receiving 2 injections	Mice receiving 3 injections	Mice receiving 4 injections	Mice receiving 6 injections	Mice receiving 8 injections	Mice receiving 12 injections	Mice receiving 16 injections
hr.	*mg./kg.*	*mg./kg.*	*mg./kg.*	*mg./kg.*	*mg./kg.*	*mg./kg.*	*mg./kg.*	*mg./kg.*
¾	114 ×1.11	73.0 ×1.14	44.3 1.22	17.1 1.25	8.2 1.27	0.69 1.38	0.12 1.47	<0.05
1½	—	97.3 ×1.13	20.6 1.20	7.7 1.41	0.8 1.30	0.067 1.28	0.11 1.22	0.05-0.2
3	—	39.0 ×1.24	2.1 1.27	0.75 1.42	0.72 1.43	0.24 1.25	0.05-0.2	0.05-0.2
6	—	9.8 ×1.32	3.2±	1.5 1.16	<0.8	0.52 1.16	0.05-0.2	0.05-0.2
12	—	10.7 ×1.21	3.3 1.21	1.9 1.30	0.89 1.57	0.98 1.22		<0.2
24	—	58.1 ×1.23	19.5 1.25	52.6 2.16	>50.	3.3 1.54		

*The method of producing the infection, and the method of treatment, are described in the text. Of necessity, the results here given are the composite of a number of experiments carried out at different times. A total of 20-60 mice were treated at each of a series of dosage levels, varying twofold. The method used in computing the CD_{50} dosages and their standard errors has been described in a preceding paper.[3]

†The first number in each block of the table is the CD_{50} value, and the second number (×) is the antilog of the standard error of the log CD_{50}.

The inoculated muscle had usually increased approximately tenfold in the 2 hours that elapsed between inoculation and treatment.) A number of different treatment schedules were used, in which the interval between injections varied in twofold steps from ¾ hour to 24 hours, and the number of injections varied from 1 to 16. On each schedule mice were injected at each of 7 dosage levels (0.05, 0.2, 0.8, 3.2, 12.5, 50 and 200 mg. per kilogram of body weight). The experimental results are given in Table 1, in which the data are analyzed in several different ways, as discussed below.*

TABLE 2. *Effect of the Interval between Injections on the Total Number of Injections Necessary to Cure a Streptococcal Infection in Mice.*

Dosage of Penicillin per Injection	No. of Injections Necessary for Cure (CD_{50})					
	at interval of ¾ hr.	at interval of 1½ hr.	at interval of 3 hr.	at interval of 6 hr.	at interval of 12 hr.	at interval of 24 hr.
mg./kg.						
200.0	1	1	1	1	1	1
50.0	2-3	2-3	1-2	1-2	1-2	2-3
12.5	4-6	4	2-3	1-2	2-3	6-8
3.2	6-8	4-6	2-3	2-3	3-4	>8
0.8	8-12	6-8	3-4	4-6	>12	—
0.2	6-8	6-8	8-12	8-12	12-16	—
0.05	12-16	>16	>16	>16	—	—

Experimental Observations

Mice weighing 18 to 22 gm. were inoculated intramuscularly with 4×10^6 beta-hemolytic Group A streptococci (C-203 strain of *Streptococcus pyogenes*) in a volume of 0.15 cc. The virulence of the strain had been maintained by passage through mice two or three times weekly for three years. In the absence of treatment, the organisms multiplied rapidly in the inoculated muscle, there was a generalized infection, and the mice died in 2 to 5 days. In the present experiments, treatment was begun 2 hours after inoculation, aqueous sodium penicillin G being used, also in a volume of 0.15 cc. and also injected intramuscularly, but not in the inoculated leg. (The number of organisms in

*We are indebted to Mr. Nathan Mantel for his assistance in the analysis. The experimental details, including the mortality at each dosage level in every experimental group, will be given in Table 1 of the reprint; exigencies of space precluded such detailed presentation in the paper as published in the *Journal*.

Interval between Injections

Effect on the number of injections and total treatment time necessary for cure. The effect of the interval between injections on the therapeutic efficacy of penicillin is clear if one analyzes the data in terms of the number of injections required for cure (Table 2), and thus, on the total duration of treatment (Table 3). For example, with a dose per injection of 3.2 mg. per kilogram of body weight, as the interval between injections was increased from ¾ to 6 hours, the number of injections necessary to cure 50 per cent of the animals at first decreased from 6–8 to 2–3. (This decrease reflects the fact that when the injections were repeated at intervals of ¾ hour, at the time of each injection penicillin was still present in effective concentration, and the full benefit of the preceding injection had therefore not been received.) However, when the interval between injections was further prolonged to 12 or 24 hours, the number of injections necessary for cure increased from 2–3 to more than 8. A similar effect is evident in each horizontal row of Table 2, reflecting the fact that with too long an interval between injections there was remultiplication of organisms surviving the action of the antibiotic.

The prolongation of the interval between injections had an even more pronounced effect on the time for which treatment had to be continued to effect cure (Table 3). With the same dosage per injection of 3.2 mg. per kilogram of body weight, when the interval between injections was increased from ¾ to 1½, 6, 12 and 24 hours, the total treatment time necessary for cure increased progressively from 4½ to 6 to 9, 12 to 18, 36 to 48 and more than 192 hours, respectively. A similar relation is evident on each line of Table 3.

It is clear from the foregoing data that in the infection here studied, in which penicillin can effect cure within 4 or 5 hours, the comparison of treatment schedules that are continued for approximately 4 days is not a valid test of their relative efficacy. Since an aggregate penicillin time of 4 or 5 hours suffices for cure, the 4-day schedules of necessity provide long penicillin-free intervals between injections during which the bacteria may recover and remultiply. That such remultiplication actually occurs under the conditions of the present experiment has been shown in preceding papers.[2-4, 9] Under such circumstances, one is not treating the original infection but a series of relapsing infections. The duration of treatment is artificially prolonged, and the curative dosage of penicillin is increased by permitting the bacterial population to be reestablished between injections of penicillin. The degree of such remultiplication will vary according to the size of the individual injection and the duration of the penicillin-free interval. The experiments of Schmidt and Walley,[10] who, in an experimental

TABLE 3. *Effect of the Interval between Injections on the Time Necessary for Cure of Streptococcal Infection in Mice.*

Dosage per Injection	Total Treatment Time* Necessary for Cure					
	at interval of ¾ hr.	at interval of 1½ hr.	at interval of 3 hr.	at interval of 6 hr.	at interval of 12 hr.	at interval of 24 hr.
mg./kg.	*hr.*	*hr.*	*hr.*	*hr.*	*hr.*	*hr.*
200.0	†	—	—	—	—	—
50.0	1½–2¼	3–4½	3–6	6–12	12–24	48–72
12.5	¾–4½	6	6–9	6–12	24–72	144–192
3.2	4½–6	6–9	6–9	12–18	36–48	>192
0.8	6–9	9–12	9–12	24–36	>144	—
0.2	4½–6	9–12	24–36	48–72	144–192	—
0.05	9–12	>24	>48	>96	—	—

*For example, with 4 injections repeated at 3-hour intervals, the total treatment time is taken as 12 hr., although the injections were actually completed within 9 hr.

†More than half the animals were cured by a single injection at this dosage level.

TABLE 4. *Effect of the Interval between Injections on the Curative Dose of Penicillin (CD_{50}).*

No. of Injections	Total Curative Dose (CD_{50})					
	at interval of ¾ hr.	at interval of 1½ hr.	at interval of 3 hr.	at interval of 6 hr.	at interval of 12 hr.	at interval of 24 hr.
	mg./kg.	*mg./kg.*	*mg./kg.*	*mg./kg.*	*mg./kg.*	*mg./kg.*
2	146.0	195.0	78.0	20.0	21.0	116
3	133.0	62.0	6.3	9.6±	9.9	58
4	68.0	31.0	3.0	6.0	7.6	210
6	49.0	4.8	4.3	<4.8	5.4	>300
8	5.5	0.54	1.9	4.1	8.0	25
12	1.4	1.3	<2.4	<2.4		
16	<0.8	0.8–3.2	0.8–3.2	0.8–3.2	<3.2	

pneumococcal infection of rats, compared a number of treatment schedules requiring 4 days for completion, may have been influenced by this factor.

Effect on the curative dose of penicillin. In Table 4 the experimental data are analyzed in terms of the CD_{50} levels of penicillin on varying schedules of treatment. If that table is scanned horizontally, it is seen that when, for example, 4 injections were repeated every ¾, 1½ and 3 hours, the total curative dose was 68, 31 and 3 mg. per kilogram of body weight, respectively.* However, with further prolongation of the interval between injections to 6, 12 and 24 hours, the curative dose increased to 6, 7.6 and 210 mg. per kilogram of body weight, respectively. The further increase in the curative dose as the interval between injections was increased reflects the progressive prolongation of the penicillin-free interval, and the increasing opportunity for the remultiplication of the surviving bacteria.

Effect on aggregate penicillin time required for cure. In Table 5 the curative doses given in Table 4 are expressed in terms of the penicillin time required for cure — that is, the total time for which such CD_{50} levels provided serum penicillin in excess of 0.05 and 0.02 microgm. per cubic centimeter.† The former value serves as a first approximation of the time for which the antibiotic remained at maximally effective levels at the focus of infection, and the latter is a similar measure of the time for which it remained at minimally effective levels.[4] The data in Table 5 further support the thesis that *the primary determinant of penicillin activity is the aggregate time, not necessarily continuous, for which it remains at effective levels at the focus of infection.* There were 29 schedules in which the interval between injections was not so great as to permit significant remultiplication of the surviving organisms (to the left of the heavy line in Table 5). In these 29 schedules the CD_{50} levels of penicillin had varied almost two-hundredfold, the number of injections varied from 1 to 16, and the duration of treatment from a few minutes to six days. Despite these wide variations, the aggregate time for which the CD_{50} dosage had provided penicillin at effective levels was remarkably consistent. If one uses as a yardstick the time for which the serum concentrations had remained in excess of 0.05 microgm. per cubic centimeter† (top half of Table 5), the curative penicillin time varied only from 2.6 to 5.8 hours, with a mean of 4.1 ± 0.15.‡ In half the schedules, the variation in the aggregate penicillin time required for cure was only 3.5 to 4.5 hours. If one uses as the measure of penicillin time the time for which the serum concentrations had remained in excess of 0.02 microgm. per cubic centimeter (bottom half of Table 5), the curative penicillin time then varied from 3.6 to 6.5 hours, averaging 4.7 ± 0.14 hours.

TABLE 5. *Effect of the Interval between Injections on the Aggregate Penicillin Time Necessary for Cure.*

No. of Injections	Penicillin Time					
	At interval of ¾ hr. *hr.*	At interval of 1½ hr. *hr.*	At interval of 3 hr. *hr.*	At interval of 6 hr. *hr.*	At interval of 12 hr. *hr.*	At interval of 24 hr. *hr.*
Serum concentration greater than 0.05 microgm. /cc.:						
1	3.5					
2	3.8	4.8	4.9	3.2	3.3	5.6
3	4.1	5.1	2.9	3.3	3.3	5.9
4	4.1	5.8	2.8	3.4	3.7	>11.0
6	5.2	4.3	4.1	4.2	4.4	>15.0
8	5.3	2.6	3.8	4.9	6.0	>10.0
12	4.6	4.4	4.3	4.3	>5.4	
Serum concentration greater than 0.02 microgm. /cc.:						
1	4.0					
2	4.3	5.3	5.6	3.8	3.9	6.4
3	4.5	5.4	3.6	4.1	4.1	6.9
4	4.5	5.3	3.6	4.4	4.7	>12.0
6	5.6	5.8	5.3	5.5	5.6	>18.0
8	6.2	3.6	5.1	6.4	7.68	>10.0
12	6.5	6.2	5.9	6.0		

The variation in these curative penicillin times in part reflects the experimental error in the determination of the CD_{50} levels of penicillin. In part, however, it may reflect the varying degree to which host factors acting on the surviving bacteria during the penicillin-free interval between injections supplemented the direct bactericidal activity of the drug itself, as discussed below. In any case, the relative constancy of this factor strongly suggests that the efficacy of penicillin is determined primarily

*This initial decrease in curative dose with a larger interval between injections reflects the fact that when injections are repeated at such short intervals, penicillin is still present at effective levels at the time of the succeeding injection. At a dosage that provides penicillin in effective concentration for 2 hours, 4 injections at 3-hour intervals clearly provide an aggregate penicillin time for a longer period (8 hours) than 4 injections at 1½-hour or ¾-hour intervals.

†The Group A streptococcus used in the present experiments is killed at essentially the maximum rate in vitro at penicillin concentrations in excess of 0.024 microgm. per cubic centimeter.[13] Since approximately half the serum penicillin is bound to protein, it requires a serum concentration of no less than 0.05 microgm. to provide this maximally effective level in the tissue fluids. Similarly, the minimal concentration that exerts a slow bactericidal effect on almost the total bacterial population is approximately 0.008 microgm. per cubic centimeter. To provide this in the tissue fluids would require a serum concentration in excess of 0.016 microgm. This has here been rounded off to 0.02.[4]

‡Standard error of the mean has been estimated as $\frac{\text{range}}{\sqrt{n}}$, after Mantel.[14]

by the total time for which it remains at effective levels at the focus of infection. It was only when the interval between injections was sufficiently prolonged to permit extensive remultiplication of the surviving organisms (schedules to the right of the heavy line in Table 5) that a significantly longer aggregate penicillin time was required for cure.

Effect on the curative dose of penicillin and aggregate penicillin time in schedules completed within the same period. A comparison may be made of schedules in which the total duration of treatment was the same but in which the number of injections given in that period differed (Table 6). Confirming the results previously obtained in a variety of infections,[2, 5] the more doses given within a given period, the smaller the total curative dose of penicillin. Thus, when treatment was completed within a 12-hour period, the CD_{50} for two injections at 6-hour intervals was 20 mg., that for 4 injections at 3-hour intervals 3 mg. and that for 8 injections at 1½-hour intervals only 0.54 mg. per kilogram of body weight. A similar relation is evident in each horizontal row of Table 6.

TABLE 6. *Effect of the Interval between Injections on the Total Curative Dose of Penicillin (a Comparison of Schedules Completed within the Same Period).*

Duration of Treatment	Total Curative Dose			
	in 2 subdoses	in 4 subdoses	in 8 subdoses	in 16 subdoses
hr.	*mg./kg.*	*mg./kg.*	*mg./kg.*	*mg./kg.*
3	195	68.0	—	—
6	78	31.0	5.5	—
12	20	3.0	0.54	?
24	21	6.0	1.9	1.6±
48	116	7.6	4.1	1.6±
96	—	210.0	8.0	1.6±
192	—	—	>25.0	<3.2

The probable explanation is that, with a sufficiently sensitive organism, multiple small doses of aqueous sodium penicillin are just as effective in providing the bactericidal concentration for the aggregate time necessary to effect cure as a much larger dose given in one or two injections. As pointed out above, the common denominator in these widely disparate curative doses is the aggregate time for which they provide penicillin in effective concentration.

Contribution of the Host to the Therapeutic Action of Penicillin

Even in the nonimmune animal, bacteria that survive an injection of penicillin may continue to die in the penicillin-free interval between injections, as the result of host mechanisms acting on the penicillin-damaged cells. In previously reported experiments in normal mice and rabbits[2, 3] this host effect was sometimes demonstrable, but it was usually slow, of brief duration and quantitatively minor in comparison to the preceding bactericidal action of the drug. In many experiments, no such effect was observed. Thus, in a streptococcal infection in mice treated with a single injection of penicillin, there was only a slight and sometime insignificant decrease in the bacterial population after the penicillin had fallen to ineffective levels.[4, 9] In the present experiments, the host could be shown to contribute significantly to the therapeutic result, presumably by acting on the surviving bacteria during the penicillin-free recovery period,* but this

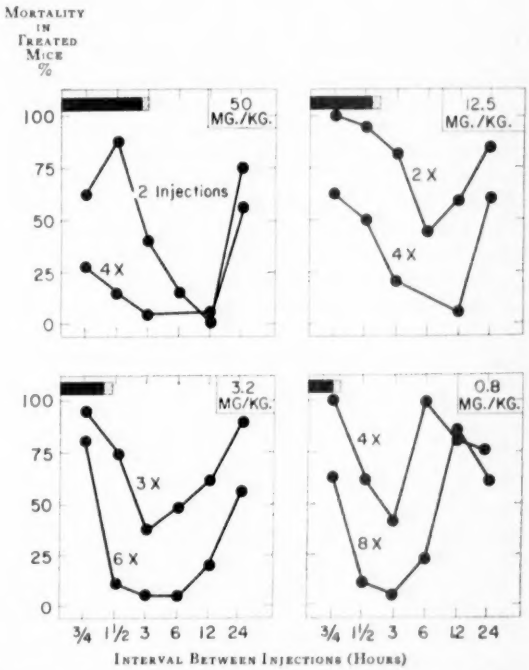

FIGURE 1. *Effect of the Interval between Injections of Penicillin on the Therapeutic Outcome (after Data of Table 1). White mice were inoculated with 4 x 10^6 Group A streptococci, and intramuscular treatment with sodium penicillin G was begun 2 hours later. The solid bar at the top of each section represents the average time for which the serum penicillin remains in excess of 0.05 microgm. per cubic centimeter at the various dosage levels[4]; the cross-hatched bar represents the additional time for which the serum level remains in excess of 0.02 microgm. per cubic centimeter.[4] These concentrations have been estimated to provide the maximal and minimal effective concentrations at the focus of infection.*

*It is puzzling to note, however, that in the nonimmune mice used in the present experiments, the bactericidal action of penicillin stopped abruptly as soon as the penicillin concentration fell to ineffective levels.[9, 4] As shown by direct subculture of the muscle focus, there was no significant decrease in the number of viable organisms in the following penicillin-free interval. The possibility may be considered that the contribution of the penicillin-free interval toward cure does not lie in the *destruction* of some of the surviving bacteria, but in their *recovery*. It is well known that actively metabolizing bacteria are more vulnerable than resting cells to the bactericidal action of penicillin, and Bigger[10] has suggested that some bacteria ("persisters") may survive the action of the antibiotic for the very reason that they are not actively multiplying. A penicillin-free interval, by allowing such organisms to resume multiplication in a focus in which the population pressure had been decreased by previous treatment, might well increase their susceptibility to a following injection of penicillin.

host factor was completely obscured if that interval was so prolonged as to permit the remultiplication of the surviving organisms.

Each section in Figure 1 shows the percentage of animals that survived a given schedule of treatment, considered as a function of the interval between injections. For clarity, only a portion of the data of Table 1 have been plotted in these figures. For purposes of illustration, a few of the curves in Figure 1 are discussed in detail, but each experimental group gave qualitatively similar results. Thus, at a dosage of 3.2 mg. per kilogram of body weight the serum concentration in mice remains in excess of 0.05 microgm. per cubic centimeter for an average period of 1.1 hours, and in excess of 0.02 microgm. per cubic centimeter for an average period of 1.4 hours.[4] These penicillin times are indicated in Figure 1 by the bar at the top of each section. Under the conditions of the present experiments, penicillin does not persist at effective levels in the tissue fluids for significant periods after it has fallen below those levels in the serum.[4] Nevertheless, when 3 injections of 3.2 mg. per kilogram of body weight each were repeated at 1½-hour intervals 26 per cent of the animals survived, whereas 62 per cent survived if injections were given at 3-hour intervals. Similarly, a dosage of 12.5 mg. per kilogram of body weight provided effective concentrations of penicillin for 1.7–2.05 hours, but the optimum therapeutic effect was achieved with injections given at 6-hour intervals. In general, in all the sections of Figure 1, it may be seen that the therapeutic effect of a given dosage lasted well beyond the time for which that dosage had provided penicillin in effective concentrations. This significant decrease in mortality effected during the penicillin-free interval presumably reflects the disposal by host defenses of a few surviving organisms that would otherwise have remultiplied to cause a fatal infection.[4, 9]

It must be emphasized that although the persistence of a therapeutic effect beyond the time for which penicillin itself is operative provides a welcome margin of safety in the use of the antibiotic, it does not establish intermittent treatment as the optimum method of therapy. Even in partially immunized animals, the bacteria were killed much faster during the time that the drug is acting than they were in the following penicillin-free interval, under the impact of host defenses alone.[9] In every experiment but one so far examined[2, 4, 5, 9] cure was effected more rapidly when therapeutically effective concentrations of the drug were continuously maintained. Furthermore, if the penicillin-free interval between injections is unduly prolonged, one runs into the danger, evident in each section of Figure 1 and in Tables 1–6, of bacterial remultiplication, which may completely or partially vitiate the therapeutic effect of the preceding injection. In the present experiments the maximum safe penicillin interval increased with the dosage of penicillin. At a dosage of 50 mg. per kilogram of body weight per injection the therapeutic effect was materially impaired only if injections were given at intervals of 24 hours, rather than 12; at a dosage of 3.2 mg. per kilogram of body weight the reversal in therapeutic efficacy was observed with injections given at 12 hours, rather than 6, whereas at a dosage of 0.8 or 0.2 mg. injections repeated every 6 hours were significantly less effective than the same dosage given at 3-hour intervals.

Discussion

It has been general experience, in both animal experiments and man, that penicillin need not be continuously maintained at effective levels at the focus of infection to achieve cure. It is, however, equally clear that bacteria are killed most rapidly during the period of penicillin action.[3, 4] If the antibiotic concentration is allowed to fall to ineffective levels between injections, the surviving organisms either remain constant in number during that interval or are killed at a relatively slow rate by the host defense mechanisms.[2-4] In keeping with these observations, it has here been shown that the time necessary for cure is unnecessarily prolonged if the penicillin is given so infrequently that there is a significant interval between injections during which the antibiotic is not present in effective concentrations (Table 3). Furthermore, with an excessive penicillin-free interval the surviving bacteria may recover from the toxic effects of the drug and resume multiplication. To effect cure, then, requires larger doses of penicillin or longer treatment than would otherwise have been necessary (Tables 4 and 5). The results with an infection due to a Group A streptococcus thus confirm and extend those previously obtained with *Diplococcus pneumoniae*, *Treponema pallidum* and a Group B streptococcus.[2]

The time for which the penicillin concentration at the focus of infection may remain below the effective level without endangering the therapeutic outcome varies with the penicillin dosage. Thus, in the streptococcal infection of mice here studied the "safe" penicillin-free interval between injections was only 3–6 hours at a dosage of 0.2 or 0.8 mg. per kilogram of body weight per injection, but was 12 to 24 hours at a dosage of 50 mg. per kilogram. (Table 2 and Figure 1.). Moreover, the danger posed by bacterial remultiplication is obviously greater with a rapidly multiplying organism and a fulminating infection than it is with an organism that multiplies only slowly, because of an inherently long generation time (for example, *T. pallidum*), because of unfavorable conditions for growth at the focus of infection or because of host defense mechanisms that limit the net rate of multiplication.

The present data indicate that penicillin is most rapidly effective if the concentration at the focus of infection remains continuously in excess of that necessary to kill the particular organism at the maximum rate. Such continuous levels could be

provided by a continuous drip, or small doses of aqueous sodium penicillin repeated at intervals of approximately 2–4 hours; or by massive doses of aqueous sodium penicillin repeated twice or three times daily by a repository form of penicillin injected once or twice daily (for example, procaine penicillin in water), twice weekly (by means of procaine penicillin in oil with aluminum monostearate) or once every seven to fourteen days (with debenzylethylenediamine penicillin). There are, however, important differences and limitations in the therapeutic usefulness of these methods.

In terms of convenience to the patient — that is, the minimum number of injections — the easiest method of administration is a repository preparation, and the most troublesome is the repeated injection of the sodium salt at intervals of about 2–4 hours. Measured by the total curative dose in experimental infections with highly susceptible organisms, the most efficient method of administration is a repository form or repeated small injections of sodium salt, and the least efficient schedule, requiring the largest amounts of penicillin, is the administration of a few massive doses of the aqueous sodium salt. On both scores, the method of choice at first sight appears to be a repository form of penicillin. However, a serious limitation is posed by the necessity of providing a bactericidal concentration at the focus of infection, and the desirability of providing the maximally effective level. Much higher serum concentrations are necessary for this purpose than the "sensitivity" of the presenting organism implies. Such "sensitivity" tests determine not the concentration of penicillin that kills the particular organism at the fastest possible rate, but rather the concentration that prevents visible growth under the arbitrary conditions of the particular test. The maximally effective (most rapidly bactericidal) concentration is usually three to ten times this barely inhibitory concentration.[11] Furthermore, since half the circulating penicillin is bound to the serum protein,[14] the concentration of antibiotic available for diffusion into the tissue fluids is only half that present in the serum. On these two grounds alone, the serum concentration should be five to twenty times the "sensitivity" level of the organism as ordinarily defined. If, in addition, the diffusion of penicillin into the focus of infection is limited either in rate or in degree by histopathologic changes (such as abscess, cavity and necrosis) or by the anatomic location of the infectious process (as in meningitis), an even larger multiple of the inhibiting concentration must be provided in the serum to assure the presence of the maximally effective concentration at the focus of infection. It follows that a repository form of penicillin that in a dose of 600,000 units provides a blood level in excess of about 0.5 units per cubic centimeter for 12 hours will usually be maximally effective against organisms "inhibited" in vitro by 0.05 units and reasonably effective against organisms inhibited by 0.05 to 0.2 units per cubic centimeter but will be wholly ineffective against, for example, a strain of *Streptococcus faecalis* that is inhibited by a concentration of 1 microgm. per cubic centimeter and killed at the maximum rate by concentrations of 5 microgm.

In choosing between the many dosage forms of penicillin, which vary widely in their rate of absorption and, therefore, in both the duration of their action and the magnitude of the serum concentrations that they afford, the physician must consider the approximate "penicillin sensitivity" of the presenting organism and the location of the infectious process. A serum concentration ten times the sensitivity level will usually provide the maximally effective concentration at the site of infection, and the physician can use the schedule of treatment that, at the greatest convenience to the patient and himself, will provide such a serum level more or less continuously. For example, an organism killed most rapidly by 5 units per cubic centimeter would compel the physician to use massive doses of aqueous sodium penicillin at fairly frequent intervals; for an organism requiring 0.5 units per cubic centimeter 600,000 units of aqueous procaine penicillin repeated once or twice daily would probably suffice; for organisms killed most rapidly by approximately 0.1 to 0.2 units per cubic centimeter or less, 1,200,000 units of procaine penicillin in oil with monostearate repeated every 4 days would ordinarily be an effective regimen; and for highly sensitive organisms, such as Group A streptococci, *T. pallidum* or gonococci, the even more slowly absorbed dibenzylethylenediamine salt administered every 10 days would probably suffice. In each case, if the diffusion of penicillin into the focus of infection is limited by anatomic considerations, it becomes necessary to use a more rapidly absorbed preparation, providing higher concentrations in the serum than would otherwise be required.

The data here reported, and the conclusions drawn from them, apply solely to penicillin. With this antibiotic there is a maximally effective concentration, varying from strain to strain, that kills the organisms at the fastest possible rate, and even a ten-thousandfold increase in penicillin concentration beyond this maximally effective level does not further accelerate its bactericidal action. The time-dosage relations discussed above follow directly from this property. With the other antibiotics, the bactericidal effect either increases continuously with the concentration used (as with streptomycin and bacitracin) or is so slow (as with aureomycin, chloramphenicol and terramycin) as to suggest that host factors contribute materially to their therapeutic effect. With streptomycin and bacitracin the most rapidly effective schedule would, *a priori*, be one providing the maximum concentration, and for the longest continuous period, consistent with the toxicity of the drug. With the latter group of antibiotics the optimal time-dosage relations re-

main to be determined. Studies on the degree to which the host contributes to their therapeutic action, and the nature of the host effect, are clearly pertinent in this connection.

Summary

In a streptococcal infection in mice cure with aqueous sodium penicillin was effected most rapidly by the continuous provision of maximally effective concentrations of the drug. If the penicillin was given so infrequently that the concentration at the focus of infection fell to ineffective levels in the interval between injections, the time necessary for cure was correspondingly increased; and if the penicillin-free interval was prolonged to the degree that surviving bacteria could recover and remultiply, not only was the time of treatment prolonged but also a larger number of injections and a larger total dosage of penicillin were necessary for cure.

In the penicillin-free interval between injections, the host contributed slightly but definitely to the therapeutic result, presumably by disposing of some of the surviving bacteria. (An alternative possible explanation is discussed in the text.) That host participation was, however, quantitatively minor in relation to the preceding direct bactericidal action of the drug, and it was completely obscured if the penicillin-free interval was so long as to permit the interim recovery and remultiplication of the surviving organisms.

Small injections of penicillin, sufficient to provide the maximally effective level at the focus of infection, and repeated often enough to maintain the effective level continuously, effected cure just as rapidly as massive doses similarly injected.

In most of the treatment schedules studied the aggregate time for which penicillin had to be maintained at effective levels for cure (curative "penicillin time") was essentially constant, and independent of either the size of the injections or their total number. However, if the penicillin-free interval between injections was so long as to permit interim remultiplication, the curative penicillin time was significantly increased.

The implications of these observations in relation to the therapeutic use of penicillin and the optimum dosage form are discussed in the text.

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GROUP PRACTICE WITH BRANCH CENTERS IN A RURAL COUNTY*

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THE purpose of this paper is to describe a way in which some of the problems of rural medicine are being approached by the Rip Van Winkle Clinic, now six and a half years old, which is located in New York State on the east bank of the Hudson River in Columbia County.

The Rip Van Winkle Clinic was founded in an attempt to provide a means whereby people of a relatively poor rural community could be offered the best available medical care at a cost that at least 90 per cent of the people could afford. It was also designed to create an atmosphere that would attract well trained young physicians to a rural area. At the same time it was imperative that the introduction of this organization should at no time undermine the security of the already existing medical economic structure of the county. Only under these circumstances could any plan hope to set an example that might be followed by the many other rural areas comparable to Columbia County.

The county in which the Clinic is carrying on its work is almost rectangular in shape, with a slight hourglass type of constriction in the midportion. Thus, it is 30-35 miles long and 25-28 miles wide. It has a population of 42,000 people, or approximately 64.5 persons per square mile. This population density is about the same as that of 16 other counties in New York State, and about the same as that of 12 other states (Alabama, Georgia, Louisiana, Kentucky, Missouri, New Hampshire, North Carolina, South Carolina, Tennessee, Virginia, West Virginia and Wisconsin). Most of the income is obtained from dairy and fruit; however,

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the farmers of the county have a level of living index that in 1940 was 132 as compared with a level of 121 for the farmers of the rest of New York State. Columbia County in general is a county of older people, 52.7 per cent being twenty to fifty-nine years of age, and 18 per cent over sixty. Only a small percentage of the industry is owned locally.

Among important physical factors that have a direct bearing on the problems of providing complete medical coverage to this area are the supply of better than average roads that are well ploughed in winter, and the absence of natural boundaries such as rivers and mountain ranges that might divide the county. Transportation facilities are good, by and large, throughout the year.

One of the needs of the county that had to be solved before the Clinic could be activated was the provision of adequate hospital facilities. Enough contributions were made to the hospital by people interested in having the Clinic founded so that the community was inspired to take over, and with the additional help of a generous grant under the Hill–Burton Act the county is about to be served by a modern, fireproof hospital of 140-bed capacity, or approximately 3¼ beds per 1000 population.

To put the organization into effect the Rip Van Winkle Foundation was established as a tax-exempt, nonprofit-membership corporation organized under the laws of New York State. After this the Foundation was granted a license to operate a dispensary known as the Rip Van Winkle Clinic. With this as a base, the Clinic attacked the problem of how to attract well trained young physicians to a rural community.

There was a time when a single physician with black bag and such paraphernalia as could be carried in a saddlebag constituted the sum total that could be offered in medical care. Today, the scope of medicine is so far reaching and intricate that many doctors have spent their entire lifetime in the problems and care of a single field. Of necessity, this has affected the practice of medicine. Today, no physician can assume the responsibility of being qualified to give any one patient the best in all the branches of medical service. This has been appreciated with increasing conviction for many years. The solution has been that from time to time various doctors with common philosophies and mutual interests, representing specific training and talent in different fields, have banded together to practice as a group. In this way they have been able to integrate the specialization of medicine and make available to the patients the combined knowledge of several men co-operating simultaneously as a team. This is the philosophy upon which the Rip Van Winkle Clinic was founded.

To obtain such personnel it was believed that certain provisions had to be made:

The proper distribution of cases, so that men might confine their work to the field of their special interest and training.

Immediate financial security, which though limited, was sure, by the provision of a salary and fellowship.

The maintenance of an academic atmosphere by regular luncheon meetings attended by all members of the group, where difficult cases might be discussed and solutions suggested through the co-operative effort of the whole team; establishment of regular fortnightly meetings to be addressed by leaders of medicine in various fields (all doctors in the area are invited to attend these meetings); publication of a paper four times a year whereby the doctors could be encouraged to keep up with current literature and contribute articles in rotation; provision for teaching responsibilities at the nearest medical center, and freedom from appointments, so that an uninterrupted half-day each week might be devoted to this purpose; the opening, in the Clinic in Hudson, of a small but current reference library, open to all physicians of the community; and the establishment of a travel fund, which would enable the doctors in rotation to attend most of the important conferences within a reasonable distance, and report their findings at the following group meeting.

Through the mechanism of the Rip Van Winkle Foundation, enough funds became available for the purchase and renovation of an old brick dwelling into a 34-room clinic building with adequate equipment for physical diagnosis, x-ray and laboratory examinations, physiotherapy and dentistry.

Today, the staff of the Rip Van Winkle Clinic is made up of 17 doctors, all of whom either have passed the American Board specialty examinations or are board eligible. Three men who were board eligible on arrival have served the necessary two years of clinical experience and successfully completed their examinations for board membership; 3 more are in the process. This has been possible only because of the emphasis placed on, and the necessary time allotted to, the academic side of practice in this rural area.

The organizing of this group of specialists automatically has answered one of the major problems of medical care in a rural community — namely, the provision of specialists' care. Before the establishment of the Clinic in Columbia County, although there was a doctor-population ratio of 1 to a little more than 1000, the services of specialists in most of the important fields were virtually nonexistent. Consequently, patients were forced to go without or at considerable expense to travel either to Albany, 40 miles to the north, or sometimes as far as New York City, 115 miles to the south, to obtain medical care in specialty fields at metropolitan rates. The Clinic today is offering to the people of Columbia County the services of specialists in the fields of medicine, surgery, pediatrics, or-

thopedic surgery, dermatology, radiology, oral surgery, orthodontics, ophthalmology, psychiatry, physiotherapy, obstetrics, gynecology and urology.

The next problem to be approached was that of distributing medical care to the outlying districts. There are many examples of group practice throughout the United States; however, by and large, these groups are equipped to give comprehensive medical coverage in only a relatively limited radius immediately surrounding the location of the group. It was believed that this fell far short of the original goal of attempting to provide complete medical coverage for Columbia County. It was thought that branch offices should be strategically located throughout the County and that specialty services should be given in these branches by the rotation of the members of the Clinic staff, who would in turn hold regular office hours throughout the week in these outposts.

The first branch was established in Hillsdale. This hamlet is located on the opposite side of the county, 19 miles from Hudson, the site of the home office of the Rip Van Winkle Clinic. The town had formerly been served by 3 doctors and then for many years by 2. However, for the preceding three years there had been none. Accordingly, the first branch was formally opened in July, 1950.

Most unexpectedly during the same year, 1 of the doctors serving Philmont (a mill town of approximately 1800 people, 10 miles from Hudson) died. Only after the town realized that it was in need of additional medical care and a committee of citizens had been formed to look for another doctor did the Clinic offer to establish a second branch.

Each of these branches is served by a dentist and a resident internist. This doctor, although limiting himself to internal medicine, serves as the family physician to the patients of the area. He is not obliged to assume responsibilities outside his field. Although he may take care of minor lacerations, sprains and abrasions, he has at his command the services of the entire Clinic team, of which he is an integral part. By the rotation of the other members of the team, these outposts are being offered the services of qualified specialists in the fields of medicine, surgery, pediatrics, obstetrics, gynecology, psychiatry and dentistry. Services of a more limited nature, such as dermatology, orthopedic surgery, orthodontics and ophthalmology, are available to patients in Hudson, which can be reached from any part of the county in not more than thirty minutes.

The degree of utilization of these branches is suggested by the fact that in a little more than two years Hillsdale is now carrying 1873 patients, and Philmont 1577.

The next problem that the Clinic attacked was that of providing medical care at a cost that approximately 90 per cent of the people could afford. It was believed that a much more wholesome situation exists when so-called private medicine is made available to the large, broad base of the economic pyramid rather than when a high fee schedule is maintained, available only to the upper but rapidly diminishing segment of the same pyramid, and the lower brackets are cared for as so-called free patients. To bring this about, the Clinic established a fee schedule that, in general, was equivalent to the full-rate patient of the so-called free outpatient department in New York City. No means test has ever been applied. The Clinic believes that patients are divided into those who can pay and those who cannot pay. The Clinic has made a practice of extending twenty-four months of credit to those desiring this time to meet their obligations. Today, the fee schedule is on a general level with Blue Shield, Workmen's Compensation and Veterans Administration allowances. Between the 90 per cent able to meet these obligations and the 3.5 per cent who are on some sort of welfare support lies the intervening group, composed of either farmers who because they own their farm or some stock or equipment are unwilling to take the pauper's oath necessary to receive public assistance or wage earners with large families, both of whom represent the medically indigent. The dispensary operated by the Foundation through the Clinic has provided in six and a half years approximately $88,000 worth of free care to this group. No person has ever been refused medical care for financial reasons.

One of the corporate purposes for which the Foundation was organized was the furtherance of preventive medicine. On February 13, 1947, at the request of the American Cancer Society, the Rip Van Winkle Clinic opened the first detection center in upstate New York. This has been developed to the point where today it is recognized by the American College of Surgeons as a tumor diagnostic clinic. It was believed at the start that when the cancer-detection center was finally evaluated its contribution to medicine would not have been the 1 or 2 per cent of actual cancer discovered. Instead, it would have been the education of the public to a keen appreciation of the value of a checkup that is not only periodic but also thorough, and the education of the doctor to the realization that nothing short of the most complete and careful examination can fulfill his obligation to discover early asymptomatic disease. Therefore, a complete type of examination was introduced.

As an outgrowth of the work of the tumor diagnostic clinic and in keeping with the policy of preventive medicine, a so-called annual-review program was instituted. This examination, which formerly required three days and then two and is now completed in one day, is considered to represent the most thorough survey that is practical. It is

especially designed for the person who today is the forgotten man in medicine, the so-called symptom-free adult. This examination consists of the following procedures: complete history and physical examination; laboratory study (blood count, sedimentation rate, blood serologic test, urinalysis and examination of stool for blood, ova and parasites); x-ray films of chest, abdomen and gall bladder, gastrointestinal series and barium enema; oral examination by a dentist, including full-mouth x-ray films; electrocardiogram; proctoscopy; Papanicolaou smear of cervix; laryngoscopy (indirect); visual examination with Orthorater; Cornell psychologic screening; and a conference with a psychiatrist (optional).

This examination, unfortunately, has not been widely accepted by the people in the county, probably because of the cost. About 90 per cent of the candidates for this examination come from New York City. Three corporations are now offering this examination to their executives. This service in preventive medicine represents an unlimited horizon.

I want to mention in particular the work of the mental-health section, which is a vital part of the comprehensive medical care being offered to this rural community. The need for this service can be readily appreciated when it is understood that the Clinic is in the center of an area, the nearest psychiatric service to which is approximately 40 miles to either the north or the south and 80 miles to either the east or the west. Today, the mental-health team, consisting of a psychiatrist, child psychiatrist, clinical psychologist, and psychiatric social worker, attempts to meet the growing demand for services. The inclusion of these services as an integral part of the group has helped to make the concept of comprehensive medical care an accomplished fact. It is domesticating the name of psychiatry in this rural community and making possible, through the completely wholesome and already acceptable environment of an all-purpose medical clinic, the acceptance of psychiatric help for those in need, and above all the introduction of preventive psychiatry.

This, in general terms, traces from its origin the development of the organization as it exists today. At times progress has been discouragingly slow. The establishment of the organization has not been without difficulties, nor has the leadership been free from errors. By trial and error certain conclusions have been reached. Certain difficulties remain that are fundamental, and their solution is not yet apparent. I believe it is of importance to review one or two of these situations.

Among the errors was the attempt made to include in the original group 2 local general practitioners with large practices. The only method of reimbursement acceptable to these men was a percentage of the funds collected for their individual accounts. Two things rapidly became apparent: that if members of the staff were to be paid on a percentage basis they automatically became as competitive as though occupying offices on opposite sides of the street; and that any remuneration on a percentage basis, whether between individuals in a department or between departments themselves, was a deterrent to ease of referral.

A second error in this decision was the thought that it would ever be possible to change men accustomed to a large-volume type of practice to the method of practice, or way of life, demanded by the group philosophy. After a morning of house calls and hospital rounds, 35 to 45 patients would be seen in the afternoon office period, which frequently necessitated booking 3 patients every fifteen minutes. Every evening, home calls were made until 9 or 10 o'clock or later. Here was symptomatic medicine being carried on with great intensity. The pace was unbelievable, and the returns as recorded over the accounting machine staggering. Yet it left much to be desired from the Clinic's point of view. Discussion meetings could not be attended, no teaching could be carried on, charts could not be maintained, fortnightly meetings were missed more often than not, and no articles could be written for the Clinic's publication. It goes without saying that well established doctors have already set for themselves their standard of living, their insurance and annuity programs and many other fixed obligations that cannot readily be altered at a later stage in life. To have expected these men to practice a different kind of medicine at a necessarily greatly reduced income was entirely illogical. After sixteen months both men retired to the separate offices from which they had come originally, and with them also departed percentage reimbursement in medicine. It gave rise to the present policy of remuneration — namely, that men of equal training who are devoting an equal amount of time and effort and have served an equal number of years should be paid in equal amounts.

In another case I failed to realize that although a doctor may be tremendously able, he may not be temperamentally suited to be a part of a team effort, which calls for the subordination of personal distinction to the good of the group.

I believe that three present difficulties should be mentioned. The first deals with public relations with the community. At the onset there was a considerable amount of skepticism on the part of the public regarding the type of medical care that could be derived from a group. This skepticism, little by little, has been replaced by confidence in the security of a group of doctors functioning as a team. At the start a great deal was heard from the residents, who wanted the good old general practitioner who could deliver their babies, take out their appendixes, treat their coronary occlusions

and comfort them in their sorrows. The realization on the part of the public that today it is the internist who is acting as the personal or family physician is being gradually accepted, especially by the younger people in the community. The graph of the rate of growth, which is now rising at an angle of about 40°, substantiates the fact that even in a conservative community the transference can gradually be made from the dream of the general practitioner of the past to the realism of the well trained internist of the present, who though limiting his work to diagnosis and therapeutic medicine, functions in the all-important capacity of the personal or family doctor of today. It is the internist who is the keystone of group medicine. As time and public education bring a fuller understanding of the availability of a family doctor within the structure of a group, one of the misconceptions associated with group practice will have been eliminated, and the most important difficulty with community public relations will have been resolved.

The second deals with the problems of public relations with fellow practitioners who are not members of the group. In this department, I regret to say, the greatest failure has been encountered. In spite of the facts that each man in the Clinic today, excluding specialists such as psychiatrists and orthodontists, represents a replacement and not an additional physician in the area, and that the establishment of branches has been limited to the need for replacement so that the existing medical economic structure of the county would not be jeopardized, the Clinic has been viewed with suspicion and resisted vigorously.

This is perhaps understandable since, first of all, the introduction of group practice represents a change, and in any society there are those who fear a change. It is a step into the unknown. It may lead to centralization of control. It may lead to an undermining of outside physicians' economic security as the advantages of comprehensive medical care become more widely appreciated. Furthermore, many doctors, especially in a rural area, have a possessiveness toward their patients. Apart from the financial implications, there is a real emotional force associated with this possessiveness, which can have both desirable and undesirable effects. When patients come independently to the Clinic for care and treatment, a fact soon known in the intimacy of a rural area, bad public relations are apt to result with the doctor who formerly attended these people. It is a deep underlying resentment that is not soon forgotten. When patients are referred for diagnosis by doctors within the county every effort is made to maintain the confidence of the patient in the referring physician, and to see that the physician is promptly advised of the findings of the diagnostic procedures in the Clinic. Also, every effort is made to see that this patient returns to the doctor for care and treatment. This has not always been easy. As other diagnostic groups set up throughout the country have learned, patients regard the source of medicine that can diagnose their ills as the one that can best treat those ills. Here is a further source of strained relations.

Finally, there is always the problem of remuneration of physicians, which should be commensurate with the value of services rendered. In any group in which the fee schedule is maintained at a level comparable to that of the Rip Van Winkle Clinic and in which, at the same time, a high quality of medical care is given, returns will never be large. However, there are fortunately other remunerations, which cannot be measured in terms of taxable income. Group practice in a rural area will always be desirable for those who sincerely and honestly enjoy this way of life for themselves and their families, and who can find compensation in the dignity of simplicity. I believe these observations have a place in any complete description of the joys and sorrows of the establishment of a rural group.

What of the future? It is planned eventually to have four more branch offices. When this has been accomplished, all but a few people in Columbia County will be within five miles of a Rip Van Winkle office. The rate of establishment of these branches, however, will be limited to the need for replacement of doctors in these communities. It is not proposed to expand beyond the limits of the county. Although many patients from a radius of 40 to 45 miles are now being treated, it is believed that the Clinic can best serve the cause of medical care by encouraging similar organizations to be established in surrounding counties.

As long as the ability of a doctor to support his family is dependent on a fee-for-service basis, preventive medicine will never be the driving force in his life, and public-health services will always be resisted for fear of encroachment. Furthermore, it becomes more and more obvious that this "piecework" method of remuneration encourages unnecessary procedures and in many cases is a deterrent to medical care of a high quality. Not until medicine is practiced on a fee-per-capita in place of a fee-for-service basis will the full potential of physicians be turned in the direction of preventive medicine, and public-health services both encouraged and welcomed. As soon as practicable, some sort of prepaid plan will be offered to the people of Columbia County on a fee-per-capita basis through the Rip Van Winkle Clinic.

Summary

The Rip Van Winkle Clinic, in six and a half years, has provided in Columbia County, a relatively poor rural community, diagnostic facilities located in the city of Hudson. The staff of the Rip Van

Winkle Clinic is made up of 17 specialists. It is demonstrating that today it is possible to attract well trained physicians to a rural area. It is also proving that through group practice specialists working as a team can give complete medical coverage, including specialty care, to a poor rural community at its doorstep by the establishment of branches strategically located throughout the county served. It has shown that medical care of high quality can be offered at a fee schedule that 90 per cent of the people of such a community can afford and are willing to meet. Such a project can be self-sustaining, once the plant and facilities have been established.

The conclusion is reached that preventive medicine and public-health services can best be furthered by a fee-per-capita remuneration of physicians. The Clinic is building a framework in which a voluntary prepaid plan of medical care, functioning on a fee-per-capita basis, can readily be incorporated. It is carrying on an active and growing service in preventive medicine.

HAZARDS IN THE TREATMENT OF CARDIAC DECOMPENSATION*

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THE results of activity in cardiologic clinics and laboratories during the past three decades were apparently foretold in the Book of Daniel, which prophesied (**xii**:4): "Many shall run to and fro, and knowledge shall be increased." So thoroughly have the data of cardiology been discussed in publications of the past thirty years that any additional comment risks arousing the ghost of Francis Bacon to reiterate his complaint made in *The Advancement of Learning* (1605): "I find great repetition, and but little new matter, in the writers of physic." Another of Bacon's comments about medicine might serve as the text for a discussion of congestive heart failure: "For as the subtilty and variety of the subject afford many opportunities of cure, so likewise a great facility of mistake." One aspect of the treatment of congestive heart failure that deserves repeated emphasis is the harm that may be caused by therapy injudiciously or erroneously applied; some physicians occasionally come close to killing their patients with kindness.

DIGITALIS

The common manifestations of digitalis intoxication — that is, nausea and vomiting, bigeminy and heart block — are well known. The possible occurrence of less common symptoms, such as diarrhea and visual disturbances, should be remembered at all times. Some rare cardiac disorders caused by administration of excessive amounts of digitalis must also be borne in mind. Digitalis has strong vagal effects, one of which may be the production of auricular fibrillation. In other cases the vagal action may cause slowing of the heart rate to below 50 per minute, with the resultant precipitation of Stokes–Adams attacks. This phenomenon is rare but is most likely to occur in patients who are unable to increase the cardiac stroke output markedly, owing to severe myocardial disease or valvular stenosis. Another aspect of digitalis therapy that might be mentioned in passing is an error of omission rather than of commission: many physicians forget that some patients become de-digitalized gradually, unless redigitalized (cautiously) three or four times a year.

BED REST

The last decade has seen the emergence of a conflict among authorities concerning the value and harm of bed rest for patients with congestive heart failure. In the first place, the purpose of rest should be understood as avoidance of exertion, and not the maintenance of complete immobility or of any specific position. Moreover, few if any cardiologic authorities ever recommend rigid restriction of patients to bed; a comfortable reclining chair in any part of the house serves as well. Secondly, clinical experience shows that unduly prolonged rest causes muscular flabbiness and, in some cases, psychologic changes that may be more disabling than well treated congestive heart failure.

If these limitations are accepted, there is no reason to derogate traditional ideas about rest in the treatment of cardiac decompensation. The belief that bed rest of itself causes deep femoral phlebitis and subsequent pulmonary infarction is not securely founded in controlled observation; other known factors that should be considered as favoring the development of this condition are extreme degrees of stasis associated with excessive use of barbiturate drugs, hemoconcentration during overenthusiastic diuretic therapy and changes in blood clotting caused by barbiturate drugs or by the excessive production of epinephrine that occurs during severe physical or emotional shock or discomfort. The

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problem of femoral phlebitis in the bedridden requires much study, and statements that the bed alone is to blame are as yet unproved. In this connection it is important to bear in mind that bed rest in the waking state may have markedly different effects from bed rest during sleep or stupor.

Morphine

The immediate and strikingly beneficial effect of morphine on cardiac dyspnea is well known. This action is presumably due to amelioration of discomfort in general and also to diminution in respiratory activity in some cases. Untoward effects are also well known; these include excessive — in some cases, fatal — depression of respiration in chronic cor pulmonale, vomiting or cutaneous itching in sensitive persons and impairment of bladder function in patients with enlarged prostate glands.

Other undesirable consequences of the action of morphine are equally important but less generally recognized. One that has received recent recognition in the clinical literature is the action of the drug in inhibiting mercurial diuresis; it is now evident that there is little point in giving mercurial injections to patients who are under the influence of morphine. Another undesirable action of the drug — one that has been emphasized only in the physiologic literature — is its hypotensive effect. Morphine in doses of about 15 mg. has no effect on the circulation in recumbent patients; however, when subjects given morphine are tilted up with feet dependent, a hypotensive syncopal attack may occur. One can only speculate about how often morphine precipitates collapse in patients with myocardial infarction or pulmonary edema who are placed with the head up and feet hanging while being transported from home to a hospital. Also, shock may be precipitated in some patients placed in such a position for the treatment of pulmonary edema. Patients with cardiac failure who are sick enough to require morphine should be subjected to as little handling as possible.

Oxygen

The common use of oxygen in the treatment of manifestations of cardiovascular disease is usually beneficial; in some circumstances, however, oxygen may have harmful effects. Mixtures containing 90 to 100 per cent of oxygen may cause a decrease in vital capacity when administered continuously for twenty-four to thirty-six hours. The gas in high concentration is also irritating to the respiratory mucosa. In occasional cases it may favor the development of atelectasis. This phenomenon is apparently owing to the washing out of the nitrogen in the pulmonary alveoli — a process that requires less than seven minutes in the normal lung and less than fifteen, as a rule, in the abnormal lung. Alveoli containing no nitrogen will, if temporarily blocked by secretion, collapse markedly when the oxygen in them is rapidly absorbed; the presence of less readily absorbable nitrogen in alveoli normally causes only a slight amount of immediate alveolar collapse when the small bronchi are temporarily plugged. A rare complication of the prolonged use of high concentrations of oxygen is the vasomotor collapse that may occur when the patient suddenly resumes breathing room air; oxygen in high concentration has a systemic vasoconstrictor effect (of unknown mechanism), and during its action normal vasomotor mechanisms may be depressed, leaving the patient without protection against hypotension when the oxygen is removed. All these untoward effects are consequent to prolonged exposure to very high concentrations of oxygen and do not occur at concentrations below 80 per cent.

The harmful effects of oxygen therapy in cor pulmonale are also worthy of comment; they may be precipitated in this condition by concentrations as low as 40 per cent. Chronic anoxia and carbon dioxide retention of severe degree are present in cor pulmonale. The respiratory center becomes accustomed to this degree of hypercarbia in only a few days, and the excess carbon dioxide in the blood ceases to act as an effective respiratory stimulant; respiration is maintained largely by the stimulus of anoxia. Relieving the anoxia by means of oxygen therapy depresses respiration to such a degree that carbon dioxide retention increases markedly. The resulting acidosis (or possibly the carbon dioxide itself, which in high concentration is a narcotic) causes coma, or in some cases confusional psychoses. Another acidotic mechanism — one causing tissue acidosis — acts in patients given excessive amounts of oxygen. The transport of carbon dioxide away from the tissues depends in large measure on the development of basic properties in hemoglobin when it is changed from acid oxyhemoglobin to reduced hemoglobin. The therapeutic use of oxygen in high concentrations may cause so much of the gas to dissolve in the plasma that venous blood contains a decreased amount of the basic reduced hemoglobin; tissue carbon dioxide retention results. All the acidosis-producing effects of oxygen administration are rapidly reversed when room air is breathed.

Aminophylline

The action of aminophylline in causing gastric irritation needs no comment here. In addition, it is a potent relaxer of smooth muscle. It greatly relaxes constricted bronchi and has a less striking effect on the smooth muscle of blood vessels; its effects on other smooth muscle are negligible in doses used clinically. The drug must be given intravenously if a rapid dilatation of constricted bronchi is desired, as in cardiac asthma. The aim is to obtain a circulating concentration of the drug large enough to relax bronchial muscle but not enough to dilate vascular muscle. Rapid injection of aminophylline may cause so much vasodilatation

as to precipitate collapse or even death. Slower but still excessively rapid injection may cause lesser degrees of peripheral arteriolar dilatation, resulting in an increase in cardiac output (and work) and the development of cardiac pain in patients with rigid coronary arteries. This reaction may at first seem paradoxical, since aminophylline is used for the treatment of anginal pain, being given by mouth, however, in doses far too small to cause generalized vasodilatation.

Ammonium Chloride

Ammonium chloride may cause gastric irritation, the manifestations of which may confuse the picture in a patient in the process of digitalization. This effect may be obviated by the use of enteric-coated tablets of the drug, but it must be remembered that in occasional cases this coating may not dissolve in the intestinal tract; a simple way to test this is to measure the urinary chloride output after the drug has been given.

The action of ammonium chloride as a diuretic given alone is largely based on the transformation of ammonium ion to urea, with the resulting liberation of chloride ion that carries sodium with it as it is excreted. This mechanism ceases to act after a few days and the drug is excreted unchanged; the diuretic effect of ammonium chloride, never great, is only of short duration. However, the use of the drug is important in patients given mercurial injections, in that it prevents the development of excessively low blood chloride levels, thereby augmenting diuresis and reducing the tendency to refractoriness. When ammonium chloride is given to patients with impaired renal function, a significant rise in blood urea level occurs. It is not established that this is harmful. However, the giving of very large doses of the drug, such as 15 gm. a day to normal subjects or small amounts for long periods to patients with renal insufficiency, leads to the accumulation in the blood of ammonium ion in concentrations toxic to brain tissue; psychosis or coma may result.

The prolonged use of ammonium chloride in patients with renal insufficiency may also cause sufficiently severe acidosis to produce coma. Even the mild acidosis that regularly develops in patients given 8 to 10 gm. of ammonium chloride a day may have undesirable effects; cardiac output is increased, and a strain thereby imposed on the heart. The acidosis may aggravate dyspnea. In addition, acidosis has a metabolic effect, not well understood at present, consisting in a depression of carbohydrate utilization. This phenomenon may complicate the regulation of some diabetic patients and in all patients increases protein wastage. The occurrence of protein deficiency in many patients with congestive heart failure is well known; it might be aggravated by the long-continued use of moderately large doses of ammonium chloride.

Mercurial Diuretics

The action of mercurial diuretics depends on their effect in inhibiting the reabsorption of chloride in the renal tubules; the increased output of chloride carries off base — chiefly sodium — and water. Frequent mercurial diureses may so markedly deplete the body of chloride as to prevent subsequent mercurial diuresis even though the patient is still edematous. This situation is easily remedied by the administration of ammonium chloride, 7 or 8 gm. of that substance being required to prevent a fall of blood chloride level during mercurial diuresis.

More serious is the development of the low-sodium syndrome, which is the result of frequent mercurial injections in a patient whose sodium intake is markedly restricted. Some patients with a lowered blood sodium concentration may become unresponsive to mercurial injections whereas others may continue to have fairly large diureses. In the latter a variety of syndromes develop — muscle cramps, confusion, stupor or a shock-like state usually unaccompanied by tachycardia. The treatment is to give a 5 per cent solution of sodium chloride intravenously, despite which an occasional patient may go on to die. Prevention of the syndrome merely involves limitation of excessively rigid salt restriction to cardiac patients who can be kept free of edema by this degree of restriction alone, without mercurial diureses.

The loss of chloride that occurs during mercurial diuresis carries off basic ions other than sodium. The loss of potassium and calcium is increased in patients depleted of sodium. The loss of calcium rarely reaches degrees sufficient to cause hypocalcemic tetany, but the depletion of body stores of potassium may be marked. Some patients actually excrete more potassium than sodium during diuresis induced while they are in a state of sodium depletion. It has been known for decades that skeletal muscle of patients with congestive heart failure contains abnormally low concentrations of potassium; whether the profound skeletal-muscle weakness of cardiac decompensation is related to this chemical change is at present a matter for conjecture. There is some evidence that potassium loss accentuates digitalis intoxication. The loss of potassium during mercurial diureses can be minimized by administration of generous amounts of fruit juices, which contain a good deal of potassium and little sodium.

The possibility of mercury poisoning need be mentioned only briefly. It occurs only — and usually in a mild form — in patients given mercurial diuretics by mouth.

Low-Salt Diets

Some patients in whom edema develops during congestive heart failure may be kept free of edema by means of rigid restriction of sodium intake without the use of mercurial diuretics. Skill is

needed in the planning of these diets, to make them attractive and to ensure that the patients receive required amounts of animal protein and components of the vitamin B complex. Use of the Karell diet imposes additional deficiencies of calories, thiamine, vitamins A and C and iron.

Severe restriction of sodium intake combined with repeated injections of mercurial diuretics can be expected to lead to the low-sodium syndrome. Patients who require frequent mercurial diuresis should be advised not to restrict their salt intake excessively; extreme restriction is best reserved for patients who can be kept free of edema without mercurial diureses.

Ion-Exchange Resins

The use of ion-exchange resins is not widespread at present but may become so. In addition to gastrointestinal upset and the acidosis caused by the ammonium chloride contained in some resins, the chief hazard is sodium depletion.

Abnormal Water Intake

Marked restriction of water intake was once practiced in the treatment of edema in cardiac disease. It is now known that this was of little help in preventing edema and might even favor its persistence owing to stimulation of the posterior lobe of the pituitary gland. In recent years forcing of fluids by mouth has been recommended by some, with the aim of obtaining the diuretic effect of water. However, it has long been known that water diuresis cannot be induced in edematous cardiac patients; excessive intake of water may produce vomiting and signs of water intoxication.

Anticoagulants

The use of anticoagulant drugs to counteract the tendency to the development of femoral phlebitis in congestive heart failure is not without hazard. The dangers of anticoagulant therapy are increased in the presence of hepatic disease; dosages should accordingly be smaller than usual in patients with engorged livers.

Tourniquets, Venesection and Positive-Pressure Respiration

Decreasing the venous return from the limbs by means of tourniquets helps to relieve pulmonary congestion and edema. However, the diminution in blood flow through the lungs is accompanied by a corresponding fall in the output of the left ventricle; in addition, the blood volume decreases as a result of increased filtration into the tissues of the extremities. Shock is sometimes precipitated by the use of tourniquets. Tourniquets also cause a marked reduction in cutaneous blood flow in the extremities and thereby impair heat dispersal; the use of tourniquets for several hours may induce a fever that may be misinterpreted. Another effect that may be misleading is a sudden increase in respiratory activity that occurs shortly after the tourniquets are released; this phenomenon is due to the entry into the circulation of blood containing large amounts of lactic acid and carbon dioxide accumulated during a period of stasis in the extremities. This brief period of hyperpnea should not be considered an indication for the reapplication of tourniquets.

Tourniquets commonly cause the development of edema in the extremities, owing to increased filtration from the obstructed vessels. In addition, some mechanism that causes over-all water retention apparently operates; this mechanism has not yet been defined. It is evident that prolonged use of tourniquets enhances peripheral edema and might theoretically favor the accumulation of pulmonary edema in one way while diminishing it in others.

Venesection and positive-pressure respiration decrease cardiac output and blood volume and thereby may precipitate or aggravate shock. The difficulty of performing venesection in patients in incipient or mild shock has saved many lives.

Prolonged standing or sitting with legs dependent causes a decrease in blood volume (owing to increased filtration into the tissues of the legs) and in cardiac output and accordingly affords all the hazards as well as all the benefits of the application of tourniquets.

Discussion

In some localities cardiac patients are undertreated with digitalis and overtreated with the other measures used in congestive heart failure. It is evident that adequate treatment with digitalis minimizes the need for some of the procedures discussed here. It must be borne in mind that, except for digitalis, all therapy for cardiac decompensation is symptomatic and does not improve cardiac function (except indirectly by relief of anoxia in some cases); these treatments impose abnormalities that are different from but only partly opposite to those of the disease. It is not surprising, therefore, that use of the therapeutic agents discussed above may do harm at times. On the other hand, any harm done is usually the result of excessive or injudicious use of these agents; the well informed, alert physician can prevent these hazards or counteract them quickly when they occur.

SURGICAL TREATMENT OF DIVERTICULITIS OF THE COLON

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THE purpose of this paper is to advocate a more aggressive attitude toward the surgical treatment of diverticulitis of the colon, which in the past has usually been withheld until after complications of the disease have occurred. Certain features of this condition should be considered as indications for elective resection to forestall complications. The increased safety with which such procedures can now be accomplished, owing to improvements in preoperative preparation, technical advances and better understanding of postoperative care, have made this approach to the problem increasingly desirable.

THE PROBLEM

It is well recognized that diverticulosis of the colon is a relatively common condition, the diagnosis being established ordinarily by barium-enema x-ray examination, usually as an incidental finding. These diverticula are acquired lesions and their incidence increases with the average age of the patients studied.

Such acquired diverticula, called pseudodiverticula, represent a herniation of the mucosal lining of the bowel through the muscular coats, occurring at a point of natural weakness, usually around a blood vessel leading into the base of an epiploic appendix. These are in contrast to true congenital diverticula, of which Meckel's diverticulum is the classic example, in which the pouch consists of all layers of the intestinal wall rather than of only mucosa and serosa.

Diverticula occur throughout the colon, but are most common in the sigmoid. They are usually multiple, although solitary diverticula occur occasionally in the cecum.

Most diverticula of the colon give no symptoms. However, diverticulitis develops in a certain proportion of persons with diverticulosis. The reason for the occurrence of an inflammatory process in an area of pre-existing diverticulosis is not understood. Areas of diverticulitis may develop anywhere in the colon, but in the vast majority of cases the inflammatory process is limited to the sigmoid loop.

The onset of diverticulitis is accompanied by the usual signs and symptoms of an intraperitoneal inflammatory process, with lower abdominal pain and tenderness, nausea and vomiting, fever and an elevated white-cell count. Muscle spasm may be present, and a mass may be felt, either on abdominal or on bimanual examination.

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Most attacks of acute diverticulitis of the colon subside after a period of conservative treatment consisting of bed rest, limited liquid oral intake, parenteral administration of fluids, sedation and antibiotics. In many cases long periods may go by without further symptoms; other patients have occasional recurrent, mild attacks, which are not progressive in severity and never become a serious threat to health. In still others, however, a severe form of diverticulitis, with one or more major complications, develops. Free perforation with peritonitis may occur. A more leisurely form of perforation with the formation of a walled-off abscess or of a fistula either externally or into an adjacent organ is more common. The most usual type of internal fistula is sigmoidovesical, perforations into the uterus, vagina or an adjacent intestinal loop being less common. Another complication of acute diverticulitis is intestinal obstruction due to narrowing of the lumen of the bowel by the surrounding inflammatory process. Bleeding from an area of diverticulitis is not uncommon, and massive hemorrhage occasionally occurs.

The development of one or more of these complications in a patient with diverticulitis is an extremely serious matter, frequently leading to repeated hospital admissions and multiple operations, with prolonged invalidism and disability. Even though the ultimate mortality may be low, the economic loss involved is enormous. A careful review of the records of such cases will show that in some there was sufficient warning that the disease existed in a recurrent or persistent form for a considerable period before complications developed. The following case abstract illustrates such a situation.

CASE 1 (sigmoidovesical fistula). J. P. (M.G.H. 337943), a 64-year-old lawyer, had had an attack of acute diverticulitis in 1938 requiring hospitalization for 1 week, when diverticula and severe spasm of the sigmoid were demonstrated by x-ray examination.

During the next 13 years he had occasional bouts of vague abdominal pain, most often described as an ache in the lower abdomen associated with borborygmi. He concentrated much of his attention on his own health and made frequent visits to various physicians with many and varied complaints. During these years the white-cell count had been determined on at least 50 occasions and was almost invariably in the range of 10,000 to 14,000. Barium-enema studies were done on 5 occasions, and each showed diverticula of the sigmoid and descending colon, with spasm and irritability of the sigmoid loop. No definite abdominal tenderness was ever noted. For several years the patient had had nocturia, 3 to 5 times.

On November 2, 1951, he was admitted to the hospital with a history of pain in the penis for 2 weeks and the passage of dark-brown particles and gas by urethra. An indefinite, nontender mass was present in the left lower portion of the abdomen. Cystoscopic examination failed to reveal the site of the fistula, but the continued passage of gross fecal material

by urethra confirmed its presence beyond doubt. A proctoscope could be passed only to the rectosigmoid and revealed no abnormality of the bowel to that level. Barium-enema examination showed multiple diverticula, as well as a fistula from the sigmoid into the bladder.

An exploratory laparotomy on November 10 demonstrated an inflammatory mass in the pelvis, involving the sigmoid and consistent with acute diverticulitis. It was adherent to the bladder over an area of about 25 square centimeters. The gall bladder contained several good-sized stones. A transverse colostomy was done in the right upper quadrant. Recovery was satisfactory, and the patient was discharged home on November 29.

Progress at home was very satisfactory. For the first time in years the white-cell count was consistently at a normal level. He was readmitted to the hospital, and a resection of the descending colon and sigmoid, with end-to-end anastomosis, was done on May 21, 1952, 6 months after the lower colon had been defunctioned. Preliminary cystoscopic study failed to show any fistula into the bladder, and no definite opening into the bladder was found when the bowel was freed from it. Convalescence was complicated by multiple small pulmonary emboli, treated by anticoagulants. The patient was discharged 38 days after operation.

Closure of the colostomy and cholecystectomy were carried out on September 19, with uneventful recovery.

It seems fair to say that there was evidence of a smouldering diverticulitis in this case for a period of years. The symptoms referable to the colon, however, were so confused and buried in the variety and multiplicity of other complaints that their significance was overlooked.

Surgery to Prevent Complications

Although, in the past, surgical interest has focused chiefly on the treatment of the complications of diverticulitis, it seems reasonable to reexamine the problem and to identify, if possible, certain types of this disease in which elective resection may be indicated before complications have developed. The excellent results from sigmoid resection as shown by Smithwick[1] and others, the lowered morbidity and mortality after proper bowel preparation, adequate use of blood and parenteral administration of fluids and the judicious use of antibiotics lend encouragement to this approach.

Babington[2] has advocated that all diverticula be resected as soon as they become inflamed. From what is known at present of the natural history of this disease, such a sweeping commitment to resection does not seem justified. However, we believe that by careful study of patients with diverticulitis it is possible to select certain ones in whom the disease has demonstrated a progressive pattern or evidence of continued inflammatory activity on a conservative program of medical management. We also believe that the probability of serious complications in such cases outweighs the risk of elective one-stage resection, and that these patients are entitled to such an operation. One must also add the cases in which the possibility of a coexisting malignant process cannot be satisfactorily ruled out. This doubt may rest on x-ray findings, bleeding from the gastrointestinal tract, gross or occult, cytologic studies on washings from the bowel or unexplained clinical behavior. These patients, too, are entitled to prompt surgical intervention. The presence of another major organic disease, in addition to diverticulitis, may also be an adequate indication for operation in certain selected cases.

Brief abstracts of 3 cases are given below. Each of these represents a disease pattern in diverticulitis that we have considered an indication for elective one-stage sigmoid resection. To the indications for prophylactic operation illustrated by those cases, there should probably be added any substantial suggestion, in the form of persistent genitourinary symptoms or laboratory or cystoscopic evidence of inflammation of the bladder wall, that this structure has been secondarily involved by the diverticulitis. In weighing the relative risks in an individual case due consideration must also be given to the general physical condition and age of the patient. The former would obviously influence the risk of the proposed operation, and increased life expectancy could logically be expected to provide greater opportunity for advance of the disease.

Case 2 (repeated attacks of acute diverticulitis). R.W. (M.G.H. 635049, F. H. 105653), a 50-year-old businessman, had his first recognized attack of acute diverticulitis in September, 1948, the symptoms subsiding after 1 week's hospitalization. The diagnosis was confirmed 1 month later by a barium-enema examination, which showed diverticula involving the descending colon and sigmoid, with irritability and tenderness of the proximal sigmoid and distal descending colon.

Five months later he had another attack, which was treated at home by bed rest and antibiotics and subsided in 5 days. He was then well except for an occasional mild bout of abdominal discomfort until May, 1950, when he had another, more severe attack requiring hospitalization for several days. Again a barium-enema study done after the acute process had subsided showed diverticulosis and diverticulitis, with no evidence of cancer.

The problem was discussed with the patient, and an elective resection of the sigmoid was agreed upon. Because of obesity, a preliminary program to attain a 20-pound weight reduction was proposed and carried out. On February 12, 1951, a resection of 25 cm. of sigmoid was done. This included all the colon showing evidence of inflammation. An end-to-end anastomosis without proximal decompression was easily accomplished. Pathological examination confirmed the diagnosis of diverticulosis and diverticulitis.

The patient progressed well after operation, was discharged on the 10th day and has remained well and symptom free to date.

The recurrent bouts of acute diverticulitis, in spite of all efforts at medical management, in this otherwise healthy, good-risk patient, were considered an indication for interval resection of the diseased colon.

Case 3 (persistent evidence of inflammation). D. H. M. (F.H. 111143), a 56-year-old executive, had had a typical, well documented attack of acute diverticulitis 15 years previously and gave a history of several similar milder subsequent attacks.

He was then well until February 12, 1952, when he presented himself to his physician with a 10-day history of dull pain in the lower abdomen associated with a change of bowel habits in the direction of multiple small stools instead of normal movements before and after breakfast. There was mild tenderness in the left lower quadrant, without mass or spasm. The temperature was normal, and the white-cell count was 13,800. Barium-enema examination showed diverticulitis of the sigmoid, with severe spasm and slight tenderness, and diverticulosis extending to the splenic flexure.

The pain subsided in about 5 days, but the patient continued to feel below par and the frequent small stools persisted. A small mass could be felt in the left lower quadrant. These mild symptoms continued for the next 2 months, together with a consistent elevation of the white-cell count to about 13,000 in spite of the usual medical measures, including antibiotics.

An elective resection of the sigmoid was carried out on April 15 without complications. All gross evidence of inflammation was in the free sigmoid loop and was easily removed. In addition to diverticulitis, the resected specimen showed 2 benign sessile mucosal polyps 3 and 4 mm. in diameter.

The patient rapidly regained his normal strength and energy, enjoys an unrestricted diet and is entirely well at present.

Evidence of continued activity of the inflammatory process in spite of all efforts at conservative treatment was the indication for elective resection of the sigmoid in this case. Because of the presence of polyps in the sigmoid the patient will be followed by periodic proctoscopic and barium-enema examinations.

Case 4 (persistent gastrointestinal bleeding). C.A. (M.G.H. 60426), a 56-year-old salesman, had had mild symptoms of diverticulitis for 1 year, only partially controlled by medical measures. These symptoms were not of sufficient severity to justify operation, but over a period of 6 months there was evidence of persistent gastrointestinal bleeding. Proctoscopic examination on December 12, 1951, showed bright-red blood, in small amounts, coming down from above the 15-cm. level, although there was no history of rectal bleeding. Barium-enema studies on several occasions, as well as x-ray examination of the esophagus, stomach, duodenum and small bowel, failed to reveal any organic lesion other than diverticula of the sigmoid and descending colon. Nevertheless, repeated stool examinations were strongly positive for occult blood.

Because of the possibility of a coexisting malignant lesion, in spite of the negative x-ray studies, operation was advised and carried out on July 10. Exploration gave evidence of a fairly extensive chronic inflammatory process, limited to the sigmoid colon, which was studded with diverticula and adherent to the lateral pelvic peritoneum. Diverticula were also present in the descending colon up to the splenic flexure but without evidence of inflammation. No other lesion could be found in the colon. Palpation of the stomach and duodenum was normal. Careful examination of the entire small intestine revealed a freely movable subserosal tumor, 1 cm. in diameter, 90 cm. below the ligament of Treitz, without mucosal involvement.

The tumor of the jejunum was resected and pathologically proved to be a neurofibroma. The sigmoid was also resected, including all gross evidence of inflammatory disease. Pathological examination showed diverticulitis without evidence of cancer.

No complications developed after operation. The patient was discharged 13 days later and has remained well and symptom free up to the present time.

The presence of persistent occult bleeding from the gastrointestinal tract was the indication for operation in this case, to rule out the presence of a coexisting neoplasm. Fortunately, only benign lesions were present.

Summary and Conclusions

The surgical treatment of diverticulitis of the colon has been, in the past, almost entirely limited to the treatment of the complications of the disease.

This is an inadequate and unsatisfactory approach to the problem, involving prolonged invalidism, lengthy hospitalization and multiple surgical procedures.

A more careful study of patients with this disease is advocated in an effort to discover symptom patterns or trends that will lead to detection of a progressive or recurrent nature of the pathologic process and allow surgical intervention to be instituted before complications develop.

Certain features of diverticulitis of the sigmoid are presented as indications for elective resection. Any evidence that a malignant lesion may be present in addition to diverticulitis is an indication for prompt surgical intervention.

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MEDICAL PROGRESS

ENDOSCOPY (Concluded)*

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BOSTON

ESOPHAGOSCOPY

Indications

Desforges, Aves and Strieder[58] believe that esophagoscopy is indicated in some cases of esophagogastrointestinal hemorrhage. The patients described by these authors were bleeding from some type of upper esophagogastrointestinal lesion at the time of esophagoscopy. Barium examination could not be carried out in many of these patients because of their moribund condition. However, x-ray examination during recent, previous admissions had indicated the presence of varices in only 2 of the 6 patients in whom varices were demonstrable by esophagoscopy. The exclusion of esophageal varices or bleeding from eroded areas in a hiatus hernia will go far toward establishing the rationale for surgery.

Linton[59] now believes in a direct surgical attack upon the varix by thoracotomy and ligation when bleeding is from esophageal varices.

Esophagitis

Studies on experimental esophagitis carried out by Ferguson et al.[60] on laboratory animals and human beings (cadavers) have shown that contact of acid gastric juice with esophageal mucosa, whether brought about by vomiting, regurgitation or direct application, has a prompt and devastating effect. Intestinal mucosa is much less affected. Hydrochloric acid alone in concentrations of gastric juice has a milder effect. Bile and pancreatic juice added to the gastric juice ameliorate the effect. Peptic activity in a strongly acid medium is the important factor. Increased intracranial pressure did not reproduce esophagitis. The effect seen clinically is thought to be due either to retching or regurgitation or to the relaxed cardia in comatose states. In the prevention and treatment of nonspecific esophagitis gastric juice should be kept out of the esophagus.

Gruenwald and Marsh[61] studied acute esophagitis in infants. Acute esophagitis, usually with ulceration, was found in a sixth of the infants examined in a series of 310 autopsies. Description of the lesions included a polymorphonuclear infiltration of the esophageal mucosa, and a spectacular hyperemia in the tunica propria. In many cases esophagitis seemed to be the result of shock, although no single causative factor could be found. Vomiting and hemorrhage had occurred frequently in these infants. In 1 case there was perforation into the right pleural cavity.

In a study on gastroesophageal regurgitation Lawler and McCreath[62] believed that esophagitis and esophageal ulcer are common results of persistent or frequent gastroesophageal regurgitation. Hiatal hernia may be present and was found in 34 cases out of the 56 studied.

Hiatus Hernia

In the observation of Sweet,[63] the anatomic characteristics of esophageal hiatus hernia are based on 111 operations, all of which were done by the transthoracic route. In 87 patients, x-ray studies indicated that these hiatal hernias were of the short-esophagus type. However, this was found to be true in 4 cases only after surgical exploration. Hence, the clinical classification of the short-esophagus variety is misleading and such hernias are better considered as the "sliding type." The paraesophageal type of diaphragmatic hernia has been renamed the "parahiatal type." The congenital short esophagus with thoracic stomach is not a true hernia in the surgical sense. The incidence of sliding hernia was 87 per cent, that of parahiatal hernia 6.3 per cent, and that of congenital hernia 4.5 per cent. In 12 per cent obstruction necessitated surgical intervention. Follow-up study for six months or more has shown that 87 per cent of the patients were cured of their symptoms.

Allison[64] has discussed reflux esophagitis, sliding hiatal hernia and the anatomy of repair. Of the 176 patients with sliding hernias, 63 had chronic esophageal ulcers with stenosis, 73 had macroscopic superficial esophagitis with ulceration, 21 had no visible esophagitis, and in 19 esophagoscopy was not done, or the findings were indefinite or unreliable. Of the 63 patients with chronic ulcer and stenosis, 4 were children and 59 adults (of whom 32 were men and 27 women). Of the 73 patients with sliding hernia and esophagitis but no stenosis, only 33 were operated upon, with 1 death from coronary thrombosis when the patient was walking about on the sixth day after operation, 1 recurrence of the hernia, and 1 patient with postoperative esophagitis and an incompetent cardia without anatomic recurrence of hernia. The patients who were not operated on were considered unfit for any operation, or their symptoms did not seem to justify any major procedure. Of the 63 patients with chronic ulcer and stenosis, only 15 have had

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resection with esophagojejunostomy, and all these are alive and well.

Peptic Ulcer of the Esophagus

Thomsen[65] reports that peptic ulcer of the esophagus is most common in children under ten years of age. There was coexistent gastric or duodenal ulcer in 4 cases, and in 18 others there was short esophagus. The outstanding symptom in children is vomiting. Ulceration is accompanied by a constriction that in acute cases is due to edema and inflammatory changes rather than to spasm. Esophagoscopy was done in 16 cases and was found to be positive in 11. Among the etiologic factors discussed, the action of acids on the sensitive esophageal mucosa was considered most important.

Tanner[66] says that evidence at present shows that peptic esophagitis or esophageal ulcer is due either to reflux of peptic juice into the esophagus from surgical anastomosis, incompetent cardia or esophageal hiatus hernia, with or without a short esophagus, or to the replacement of the lower esophageal mucosa with gastric mucosa so that the ulcer is really gastric, though in what anatomically resembles esophagus.

Redish and Kertzner[67] report 6 cases of peptic ulcer of the esophagus in which the diagnosis was established roentgenologically and histologically and confirmed by esophagoscopy. Absolute diagnosis of necessity rests primarily on esophagoscopy and biopsy. The circumstance of ectopic gastric mucosa, in conjunction with associated lesions within the abdomen (peptic ulcer of stomach and duodenum, diverticulosis and so forth) or lesions conceivably involving the cervical or thoracic vagi, is suggested as a possible factor in the production of peptic ulcer of the esophagus.

In a carefully written and beautifully illustrated article on chronic peptic ulcer of the esophagus and esophagitis Barrett[68] comes to the following conclusion:

> . . . the word "oesophagitis" is now a blunderbuss term used to cover many different pathological lesions; it should always be qualified by a descriptive adjective such as "reflux oesophagitis." I believe that reflux oesophagitis is common and that it can give rise to ulceration of the oesophagus and stricture formation. In contrast with this lesion is another which has always up till now been assumed to be identical with it, and which has generally been described by pathologists — as opposed to clinicians — under the heading of "peptic ulcer of the oesophagus." I submit that most of these cases are in truth examples of congenital short oesophagus . . . in which a part of the stomach extends upwards into the mediastinum — or even to the neck — and that in this stomach a typical chronic gastric ulcer can form. I urge that, as accurate surgery must rest upon accurate pathology, we must distinguish between gastric and oesophageal ulcers.

Benign Stenosis

Heterotopic gastric mucosa in the esophagus, with ulceration and stricture formation, was the subject of an unusual case reported by Bosher and Taylor.[69] The lower half of the esophagus was lined completely with mucosa of the gastric type. At the transition between squamous and gastric mucosa chronic ulceration and stricture had occurred. This anomalous condition must be differentiated from thoracic stomach and short esophagus associated with stricture formation.

Lye Stricture

Kiviranta[70] believes that liquor adulterated with lye may be the cause of dysphagia and stricture of the esophagus. Cases in which caustic soda was used for adulterating liquor (a method generally known in Finland) apparently caused dysphagia and stricture of the esophagus, as well as achylia and anemia, are reported. The etiology described may not hitherto have been reported in the medical literature.

Web

Moutier,[71] for reasons of priority, suggests the term "Kelly–Paterson syndrome" for the condition that previously went under the name of "Plummer-Vinson syndrome." He presents a comprehensive treatise covering the history, the entire literature, the symptomatology and the treatment of this rare condition. Although the Kelly–Paterson syndrome may produce a great variety of symptoms, the outstanding features are dysphagia, iron-deficiency anemia, trophic disturbances of the skin and mucous membranes, and disturbances of skin sensitivity such as paresthesias (pins and needles) and pruritus. Esophagoscopy reveals bands, membranes or folds, which cause stenosis, and atrophy of the mucosa, which appears thinned and pale; in some cases very few bands were found. According to statistical studies by various authors, there seems to be no doubt that iron-deficiency dysphagia leads to carcinomatous degeneration in a comparatively large number of cases. Multiple primary cancers of the lips, the tongue and the gums have been observed in this condition. Moutier hypothesizes that a congenital disturbance of the iron metabolism may be at the root of the disease, and that the lesions of the different organic systems such as the skin, mucous membranes, gastrointestinal tract and blood are sequelae of this constitutional deficiency.

Achalasia (Cardiospasm)

Three cases of achalasia of the esophagus in the newborn are presented by Thomson.[72] Clinical symptoms are vomiting and weight loss. The diagnosis is made by radiologic examination, and Lipiodol should be used as contrast medium. Treatment has included atropine, gavage and dilatation by soft-rubber catheter, all with variable success. In the main prognosis is good.

Olsen and his associates,[73] on the basis of their experience with 601 cases of cardiospasm, make the following conclusions:

Exact diagnosis is important. Cardiospasm must be differentiated from diffuse spasm of the esophagus, which does not respond favorably to either hydrostatic dilatation or surgical treatment. Hydrostatic dilatation at present is the treatment of choice for most patients with cardiospasm. Relief of dysphagia for periods of four to sixteen years was obtained from a single dilatation in 60.1 per cent of 452 traced cases. If one is given the opportunity of treating a second time patients for whom an initial course of treatment by hydrostatic dilatation did not permanently relieve dysphagia, the incidence of satisfactory results can be increased to 75 per cent. However, if satisfactory results are not obtained with two courses of hydrostatic dilatation, additional treatment is likely to be of little avail. It must be anticipated that about 20 per cent of the patients cannot be permanently relieved by dilatation.

Successful dilatation in a case of properly diagnosed cardiospasm depends on accurate placement of the dilator in the cardia and severe forceful dilatation of the physiologic sphincter by an expanding dilator. A previously swallowed thread permits accurate placement of the dilator and adds to the safety of the procedure. Surgical treatment should be considered for patients who fail to respond to two or three courses of dilatation therapy. Every effort should be made to carry out surgical treatment before marked changes in the esophageal wall have taken place. Less favorable results can be expected when surgical therapy of the advanced cases is undertaken.

Surgical correction of cardiospasm may destroy the sphincteric property of the cardia. The regurgitation of gastric secretions may result in peptic esophagitis, accounting for poor surgical results.

The Heller operation appears to be the most advantageous surgical technic. This procedure permits the cardia to retain some of its sphincteric property.

If the Heller operation is not feasible and one of the operations that destroy the sphincteric action of the cardia is performed an effort must be made to reduce the acid production of the stomach.

The results of the surgical management of cardiospasm at the clinic have not been very favorable for two reasons: most patients selected for surgical treatment had far-advanced cardiospasm for which dilatation therapy was impossible or had failed to give relief, and most of the operative procedures carried out permitted reflux of gastric secretions into the esophagus. The passage of time has given an opportunity to determine the late results in most cases. Peptic esophagitis and ulceration were responsible for most of the poor results.

Treatment of cardiospasm, either by hydrostatic dilatation or by surgical means, can be carried out with little risk.

Kay[74] has made observations on the etiology and treatment of achalasia of the esophagus. In conclusion, he states:

> . . . there is evidence to show that when there is degeneration, reduction, or absence of ganglion cells in Auerbach's plexus, a preponderance of sympathetic control develops; muscular co-ordination is impossible; and the circular fibers become contracted and hypertrophied to the degree of causing esophageal obstruction with secondary esophageal dilatation and hypertrophy above. This terminal esophageal obstruction can be adequately relieved by dilatation or by severing the hypertrophied circular muscle in the terminal esophageal constriction or sphincter.

Breakey, Dotter and Steinberg[75] have studied the pulmonary complications of cardiospasm in 63 cases, 17 of which are reported for the first time. It is evident that the aspiration of material from the dilated food-filled esophagus, especially at night, may cause serious pulmonary lesions such as pneumonia and lung abscess — or even sudden asphyxia. These lesions cannot be expected to respond permanently to therapy unless the fundamental lesion, the cardiospasm itself, is eliminated. Cardiospasm is a treatable disease. The present study indicates the desirability of early diagnosis and definitive therapy. The association of cardiospasm and pulmonary disease due to aspiration is sufficiently common to warrant its re-emphasis in this report. It is urged that the esophagus always be examined when pneumonia, nonspecific pulmonary infiltration, lung abscess or pulmonary lesions of obscure etiology occur.

Kramer and Ingelfinger[76] studied esophageal sensitivity to Mecholyl in cardiospasm. They believe that the abnormal esophageal motility and response to Mecholyl support the concept that cardiospasm is a neuromuscular disorder involving not only the cardia but also the lower esophagus.

Crump, Flood and Hennig,[77] in a study of the results of medical treatment of idiopathic cardiospasm, state that 69 (95 per cent) of 72 patients with idiopathic cardiospasm were satisfactorily relieved after one to three attempts at forceful divulsion of the cardia. After successful treatment the difficulty in swallowing remained minimal or completely relieved for an average follow-up period of three and eight-tenths years. Follow-up examination by x-ray methods and with the stomach tube with obturator revealed that the cardia relaxed promptly after such treatment. Motor dysfunction of the lower two thirds of the esophagus persisted after treatment, although the patient was usually asymptomatic. There were two main components in this disorder: tonic contraction of the cardia and impaired motility in the main part of the esophagus.

A follow-up study was carried out by Barrett and Franklin[78] concerning the unfavorable late results in 19 patients who were subjected to esophagogastrostomy and 6 subjected to cardioplasty for the relief of cardiospasm. The immediate results were striking, but only 4 of the 25 patients remained symptom free and clinically well. Both early and late results of these operations are discussed in detail, and the lessons learned from cardioplasty and esophagogastrostomy are emphasized. Illustrative cases are presented with roentgenograms, drawings and a table summarizing results. It is concluded that these procedures, which alter the anatomy of the lower end of the esophagus, may result in the complete disorganization of the normal mechanism that prevents regurgitation from the stomach into the esophagus. Regurgitation of this type produces an esophagitis, which may result in dysphagia, pain, hematemesis or anemia. The authors have abandoned esophagogastrostomy and cardioplasty in the surgical treatment of cardiospasm, and recommend an extramucous esophagocardiomyotomy (Heller's operation) when medical management fails.

Varices

Sengstaken and Blakemore[79] discuss balloon tamponage for the control of hemorrhage from esophageal varices. Their report describes a triple-lumen tube, carrying two balloons, which is devised for passage by naris into the stomach. While the distal balloon anchors the tip of the tube in the stomach the proximal balloon, inflated by air, presses against the wall of the terminal esophagus and compresses the veins of the coronary-esophageal junction. Pressure between 20 and 30 mm. of mercury is sufficient to control hemorrhage from esophageal varices. Bleeding was controlled by balloon tamponage in 13 of 15 patients with grave hematemesis from portal hypertension, all of whom survived surgical operations to provide a portacaval shunt.

Lorant[80] considers the present emergency medical treatment of bleeding esophageal varices in portal hypertension unsatisfactory. A new medical treatment consisting of elevation of the foot of the bed was suggested and tried in 6 consecutive cases. Bleeding was stopped immediately in at least 5 of the 6 cases.

Linton[59] advises an emergency surgical attack on acutely bleeding esophageal varices. By a transthoracic approach he opens the lower end of the esophagus and ligates the bleeding varix.

Benign Tumor

Taylor[81] reports the case of a paraganglioma that produced a nine-year history of dysphagia from compression of the cervical esophagus. This tumor simulated carcinoma of the esophagus clinically, radiologically and microscopically. The patient was alive and well nine years after the onset of symptoms, and seven years after he was first seen.

Gledhill and Morrow[82] described a ciliated epithelial cyst of the middle third of the esophagus. The cyst caused partial obstruction of the esophagus that was relieved by transthoracic excision of the lesion.

Myers and Bradshaw[83] reported 3 benign intramural esophageal tumors successfully treated by enucleation. They believe that esophagoscopy should be done to allow a gross evaluation of the esophageal mucosa overlying the tumor.

Cornell, Blumberg and Sarot[84] consider reduplication cysts of the gastrointestinal tract uncommon. They collected 20 cases reported in the literature during the last twenty-five years, to which they add a case of successful removal of an intramural esophageal reduplication cyst from a nineteen-month-old boy, after which the patient obtained relief from a brassy cough caused by tracheal compression and displacement. Microscopical examination of the cyst demonstrated ciliated epithelium, smooth muscle and mucous glands, with a histologic structure somewhat similar to that of a bronchus. Cysts of the esophagus are classified as reduplication cysts of the alimentary tract, ciliated epithelial cysts, cysts arising from islands of gastric mucosa, cystic or follicular esophagitis and retention cysts of ducts and mucous glands. Symptoms of reduplication cysts usually arise as the result of obstructive pressure on external viscera, pain from cystic distention or hemorrhage caused by compression of vital blood vessels. Surgical excision is the only satisfactory method of treatment of reduplication cysts.

Carcinoma

Ireland and Bryce[85] believe that carcinoma of the esophagus is a disease of men. It accounts for 5 to 7 per cent of all cancers in males. Only 5 per cent of esophageal cancers occur in women. Formerly, it was thought that esophageal cancers were slow growing, but now it is believed that they are a rapidly growing tumor causing death before metastasis becomes obvious. Only about 66 per cent of esophageal cancers are resectable. If carcinoma is even suspected, both radiologic and esophagoscopic examinations must be utilized to prove its absence. It is well known that one biopsy of a suspicious area may not be sufficient.

Resano[86] says that in 1000 cases of cancer of the esophagus he observed 15 cases in which radiologic examination was negative. In this paper, he reviews the causes of errors. Some tumors are not visible on x-ray films, because the radiologic examination is incomplete. Others appear too late on the films. In most cases, by esophagoscopy, the patient will be spared the fatal evolution of the cancer of the esophagus discovered too late.

Gibbon, Allbritten and Templeton[87] studied 89 cases of cancer of the esophagus and the cardia. In 67 patients the lesion was primary in the esophagus and in 22 it was primary in the stomach. The disease predominantly affects men, and its greatest incidence is in persons between the ages of fifty and seventy years. The outstanding initial symptom is difficulty in swallowing, which occurs in over two thirds of the cases. The diagnosis is readily established by roentgenography and esophagoscopy. The prognosis for patients with adenocarcinoma of the stomach appears to be somewhat more favorable than that for patients with squamous-cell carcinoma of the esophagus.

Sweet[88] has presented the results of resection and primary restoration of continuity by esophagogastric anastomosis in 254 cases of carcinoma of the esophagus and cardia during a twelve-year period ending January 1, 1951. Survival studies showed that 17.5 per cent of patients with carcinoma of the lower esophagus and cardia who had been operated upon five or more years before January 1, 1951, had survived five or more years. For patients whose growth lay in the midthoracic segment of the esophagus the corresponding figure was 4 per cent. It is suggested that this significant difference is a reflection of the fact that for anatomic and technical reasons it is not possible to perform as thorough a regional dissection when the growth lies in the midthoracic segment as when it occurs in the lower end and at the cardia. There is little significant difference in the five-year survival rate between patients whose tumor was histologically an adenocarcinoma and those whose growth was epidermoid in character. The presence or absence of lymph-node metastases in the resected specimen is of definite prognostic significance. In 42.5 per cent the lymph nodes were negative. In 57.5 per cent of the cases they were involved by metastases. The five-year survival in the patients with negative lymph nodes was 40 per cent; among those with involved nodes it was 13.5 per cent. These figures are based on all the cases grouped together irrespective of the level of occurrence of the growth.

Watson and Brown[89] state that cancer of the esophagus can be eradicated by properly planned beam-directed deep x-ray therapy. They report 4 treated cases in which at autopsy there was no evidence of cancer in the esophagus. Metastatic cancer was found in only 1 of these 4 cases.

Krebs, Nielsen and Anderson[90] studied rotation treatment of cancer of the esophagus. They state that curative effects were slight. In many cases the local tumor disappeared after x-ray therapy, but the patients died from metastases. However, palliative effects, such as greater amplitude in diet intake, relief from dysphagia and improvement in general condition, were noted in more than 70 per cent of the cases.

Gore and Lam[91] reported a case of carcinoma of the esophagus complicating cardiospasm. Since x-ray examination is notoriously difficult in the study of a dilated esophagus, which is often filled with food material, the more frequent use of the esophagoscope should be considered.

Other Malignant Tumors Involving the Esophagus

Resano and Albanese[92] report a case of primary sarcoma of the esophagus. The only sarcomas of the esophagus diagnosed during life have been by esophagoscopy with biopsy.

Lortat-Jacob and Badaro[93] described 2 primary pedunculated sarcomas of the esophagus. They found only 32 authentic observations of primary sarcoma of the esophagus reported in the medical literature.

Thorek and Neiman[94] state that only three cases of rhabdomyosarcoma of the esophagus have been reported in the world medical literature. The authors add a fourth interesting case, which constitutes the first known successful removal of a rhabdomyosarcoma of the esophagus. The patient was alive and working, one year after operation. The authors have collected and tabulated 58 proved cases of sarcoma of the esophagus, consisting of 30 fibrosarcomas, 8 leiomyosarcomas, 5 lymphosarcomas, 6 melanosarcomas, 3 rhabdomyosarcomas and 7 unclassified types.

Bichel[95] states that the gastrointestinal tract is often involved in Hodgkin's disease. Involvement of the esophagus, however, seems to be rare, although mediastinal Hodgkin's disease with involvement of the lung and spine is common. By esophagoscopic and roentgenoscopic examinations, these lesions are indistinguishable from those of carcinoma. Only biopsy can establish the diagnosis. The lesion may originate in the esophageal wall, but it is doubtful whether a case of primary isolated Hodgkin's disease of the esophagus has ever been verified. A case of Hodgkin's disease is described in which there was marked esophageal involvement with only slight dysphagia and in which the benefit obtained from irradiation therapy was impressive.

Benedict[41] reports a proved lymphoma of the esophagus in which transthoracic resection of the esophagus with esophagogastric anastomosis was performed. The tumor was primarily located in the submucosa and seemed to infiltrate the muscularis and the deeper layers of the mucosa.

Carcinoma of the thyroid gland occasionally invades the esophagus. Such a case was seen recently at the Massachusetts General Hospital. The patient was a forty-three-year-old woman who entered the hospital complaining of fever, malaise, sore throat and difficulty in swallowing of six months' duration. Total thyroidectomy was done. Carcinoma had invaded and ulcerated the esophagus. The esophageal wall was resected and repaired

at the time of thyroidectomy. The pathological report was adenocarcinoma, Grade 3, of the thyroid gland, with invasion and ulceration of the esophagus. The patient did well after operation.

Foreign Body

Belmont[96] reports an unusual foreign body that caused a complete obstruction of the esophagus in its upper third. This consisted of a gelatinous mass formed from three coated methylcellulose tablets that had become hydrated in the esophagus. Endoscopic removal of the resultant gelatinous mass eight hours after the pills were swallowed completely relieved the distressing symptoms of choking and smothering.

Another interesting case of esophageal obstruction is reported by Hinkel.[97] This presumably resulted from the ingestion of dry Serutan, a bland, granular hygroscopic substance widely used as a remedy for constipation. At the time of esophagoscopy the lumen was completely obstructed by pasty, granular, brown material that looked somewhat like brown sugar. It was sticky and cohesive and was removed with great difficulty, since the aspirator frequently became clogged. Some of the material was extracted with forceps. After the impaction had been relieved the symptoms disappeared.

Extrinsic Pressure

Gross and Neuhauser,[98] in an article on compression of the trachea or esophagus in vascular anomalies, state that endoscopic visualization of the interior of the esophagus or trachea gives valuable information in some of these cases.

Kertzner and Madden[99] report a case of cervical exostosis causing dysphagia. A survey of the literature reveals exostoses of the spine to be a rare cause of dysphagia. This condition tends to occur in older age groups. The lower cervical and lower thoracic regions are most frequently involved, presumably because of fixation of the esophagus in these areas. Symptoms are usually mild and readily controlled. Surgery is rarely indicated. These exostoses assume added significance because of the danger of esophageal perforation during endoscopy.

Malignant thymoma may cause extrinsic pressure on the esophagus. Such a case recently occurred at the Massachusetts General Hospital and is mentioned in this review by courtesy of Dr. R. R. Linton and Dr. John Cass. The patient, a fourteen-year-old schoolboy, entered the hospital because of swelling of the neck and face of six days' duration. Fever, dyspnea, wheezing and paroxysmal coughing were marked symptoms. Nausea and dysphagia were present. X-ray examination disclosed a nodular mass in the anterior mediastinum displacing the trachea and esophagus far posteriorly and to the left. Exploratory thoracotomy revealed a malignant tumor, part of which was removed with decompression of the mediastinum. The pathological report was malignant thymoma.

Bronchoesophageal and Tracheoesophageal Fistula

Kidd and Christopherson[100] present a case of broncholithiasis associated with bronchoesophageal fistula and in reviewing the literature find a report on only 1 similar case. The bronchoscopic findings were those of a mass suggesting carcinoma. This mass was later proved to be chronic inflammatory and vascular granulation tissue.

Mellins[101] encountered an acquired tracheoesophageal fistula of undetermined etiology in a thirty-five-year-old woman with syphilis and probably with tuberculosis. The fistula was satisfactorily treated by surgical intervention. The main causes of acquired tracheoesophageal fistula, in order of frequency, are carcinoma, trauma, syphilis and tuberculosis. The commonest site of the tracheoesophageal fistula is the region of the bifurcation of the trachea. A sudden sensation of strangling a few seconds after the ingestion of food or drink is the most characteristic symptom of tracheobronchial fistula. The fistula can be demonstrated by roentgenograms of the chest made after the instillation of iodized oil in the esophagus. Specimens for biopsy and culture may be taken during the esophagoscopic and bronchoscopic examination of the fistulous openings. Surgical closure of the fistula is best accomplished after an adequate course of chemotherapy and local cauterization.

Specific Infectious Diseases

Hudson and Head[102] presented a case of tertiary syphilis of the esophagus. A history of long-standing dysphagia of a painless nature, with positive serologic tests and x-ray or endoscopic evidence of intrinsic esophageal obstruction, is thought to be suggestive of the presence of tertiary syphilis of the esophagus. The treatment is primarily medical, but dilatations of the esophagus are indicated when stenoses are present. The prognosis is favorable except in patients with tracheoesophageal fistulas, whose prognosis appears favorable if aspiration pneumonitis can be prevented.

Miscellaneous Conditions Affecting the Esophagus

Benedict and Lever[103] found that the esophagus is occasionally involved in benign pemphigus of the mucous membrane resulting in web-like adhesions that narrow the lumen of the esophagus. Early recognition of the esophageal lesions is important because in their early stage the adhesions can easily be divulsed.

Gastroscopy

Gastroscopic Biopsy

Since the introduction of the Benedict flexible operating gastroscope in 1948,[104] 203 biopsies of the stomach have been taken by means of this

instrument in the Endoscopy Clinic of the Massachusetts General Hospital. No accidents and no complications have resulted. The advantages of the instrument are that biopsy of the stomach can be made under direct vision, and that aspiration of the gastric secretions and inflation and deflation of the stomach can be accomplished at will.

Benedict[105] has discussed gastroscopic biopsy in the differential diagnosis of gastritis and carcinoma. A biopsy of the stomach performed through the flexible operating gastroscope is of great value in the differential diagnosis of carcinoma and gastritis. In 5 of 10 illustrative cases a positive diagnosis of carcinoma was established by gastroscopic biopsy. In the other 5 cases diffuse gastric cancer was excluded with reasonable certainty by gastroscopic examination and biopsy. No gastroscopic examination is complete unless biopsy under direct vision is possible.

Shallenberger and his associates[106] have also used the flexible operating gastroscope and believe that indication for gastroscopy is an indication for biopsy. They state that a positive biopsy for a malignant lesion is conclusive. Biopsy through the flexible gastroscope is the best means available for establishing the diagnosis of diffuse intramural lymphoma, carcinoma or sarcoma. The flexible operating gastroscope is a safe instrument for general use. The authors believe that routine biopsy of all gastroscopically examined cases may well be more widely accepted and used in the future.

In another article on gastroscopic biopsy and correlation with clinical findings, Shallenberger et al.[107] state that routine biopsy should be a part of all gastroscopic examinations. In discussing this paper, LeSage, of Montreal, expressed his opinion that the Benedict type of operating gastroscope wll eventually replace the ordinary gastroscope, for this instrument holds a triple advantage: it provides much better vision; it enables a proper aspirating process; and, chiefly, it serves as a device for obtaining biopsy specimens.

Wirts, Carroll and Wald[108] have given their experience with the operating gastroscope. They conclude that the flexible operating gastroscope is an instrument with which multiple gastric biopsies may be performed with safety. In an experience lasting eighteen months they found that tissue suitable for histologic diagnosis could be obtained readily when the lesion was diffuse or located in the body of the stomach within reach of the biopsy forceps.

Wood and his co-workers[109] have taken part in the development of a technic for gastric biopsy, with the use of a flexible gastric biopsy tube. With this instrument fragments from the mucosa of the body of the stomach can be readily obtained, and serial studies made. The method has two disadvantages: the biopsy is done blindly and is therefore of no use for the diagnosis of ulcer from cancer, for which gastroscopic biopsy would be better; secondly, the specimen obtained is representative of a diffuse lesion in the body of the stomach. The method has its chief use in diffuse lesions of the body and fundus of the stomach when radiologic examination shows no local ulcerative or neoplastic change. It is of no value in the diagnosis of antral gastritis. Various stains are used, such as hematoxylin and eosin, hematoxylin and mucicarmine and a stain for pepsinogen granules. To date, biopsy has been attempted 370 times in the authors' clinic and it has been successful 304 times.

Doig and Motteram[110] demonstrate the histologic features of gastritis in 4 patients and briefly set forth the clinical features of each case.

Wood,[111] in an article on the value of gastric biopsy in the study of chronic gastritis and pernicious anemia, states that in atrophic gastritis there is atrophy of the acid-secreting and pepsin-secreting cells in addition to the inflammatory reaction. This may cause recurrent flatulent dyspepsia, atrophy of the tongue, constant hypochlorhydria or, more often, achlorhydria, and may be negative to a barium meal test. There may be hypochromic anemia, owing in part to blood loss to the mucosa, malnutrition and impaired intestinal absorption of iron. There appears to be little or no evidence that pernicious anemia or subacute combined degeneration of the spinal cord occurs in this group. The gastritis shows little or no tendency to heal.

Motteram,[112] in a biopsy study of chronic gastritis and gastric atrophy, summarizes his findings as follows:

> The morphology of the mucosa of the body of the stomach in 150 patients suffering from a variety of dyspeptic symptoms and in whom an opaque meal showed no gross abnormality is described. Changes, when present, could be grouped into two broad categories: superficial gastritis, without atrophy of tubular epithelium, and more deeply extending gastritis, with atrophy of tubular epithelium. Mucosa from patients with superficial gastritis due to excess of alcohol returned to normal after withdrawal of the alcohol. In 43 cases of pernicious anemia, complete or almost complete tubular atrophy, combined with prominent intestinal metaplasia and absence of wandering-cell infiltration, made up a pattern that was distinctive for this disease. Adequate liver-extract therapy failed to alter these mucosal appearances.

Doig, Funder and Weiden[113] made serial gastric-biopsy studies in a case of duodenal ulcer treated by deep x-ray therapy. A profound reaction of the gastric mucosa to irradiation occurred, with subsequent resolution. The course of this reaction over a period of four hundred and seventy-five days is described. The findings of serial determination

of gastric secretion of hydrochloric acid and pepsin in relation to various stages of the reaction of the mucosa are presented and discussed.

Doig et al.[114] discuss the value of gastric biopsy in the early diagnosis of subacute combined degeneration of the spinal cord. They consider that histamine-fast achlorhydria is a constant finding in this condition, and gastric biopsy in their cases has shown corresponding atrophic changes in the mucosa of the body of the stomach. The appearance of the gastric mucosa is reasonably constant. There is always thinning, with atrophy of the pepsin-secreting chief cells and the acid-secreting parietal cells. This atrophy may be complete, or a few scattered remnants may survive. Metaplasia of the epithelium to an intestinal type, with plentiful mucus goblet cells, is often extensive. The stroma may show some wandering cells of mononuclear type, but polymorphonuclear leukocytes are always absent or scanty.

Gastritis

Findley, Kirsner and Palmer[115] made a follow-up study of 100 patients with atrophic gastritis without pernicious anemia. These patients were followed for five to fourteen years (average, eight and a half years). Fifty-four of the patients had follow-up gastroscopic or roentgenologic examination, or both. Although benign-appearing gastric polyps were discovered in 2 cases six and nine years after the initial diagnosis of atrophic gastritis, no malignant tumors were detected. None of these patients were known to have developed pernicious anemia. Of 42 patients followed five to fourteen years with gastroscopic examinations, atrophy of the mucosa appeared unchanged in 23, more pronounced in 13 and improved in 6. Gastric secretion in response to histamine was measured at intervals of five to fourteen years in 28 patients. The acid output declined in 14 of the 17 patients who initially secreted free acid.

Molofsky and Hollander,[116] reviewing the gastric findings in pernicious anemia, state that during relapse, gastroscopic observations reveal changes typical of atrophic gastritis of varying degree. During remission after treatment with liver, the mucosa may be restored in variable degree to a normal gastroscopic appearance, but whether this represents a restitution to histologically normal mucosa has not been demonstrated.

Palmer[117] studied the morphologic consequences of acute exogenous (staphylococcal) gastroenteritis on the gastric mucosa. Gross gastroscopic observations were made on the stomachs of 42 patients during and shortly after an attack of acute staphylococcal food poisoning, and in 24 of the cases mucosal tissue was biopsied for histopathological study. The observations were made at intervals, from five to two hundred and eighty hours after the onset of symptoms. During the acute illness and for a period of one to three days thereafter, gastroscopic examination revealed the six characteristic changes of acute exogenous gastritis: patchy mucosal hyperemia, regional edema, muscular irritability, erosions, petechiae and purulent exudate. Patients with acute exogenous gastritis who were gastroscoped again forty-eight hours or more after the first examination were found to have normal stomachs; all the 19 patients who were gastroscoped more than eighty hours after the onset of symptoms had normal stomachs. The biopsied tissues formed a series that demonstrated a short-lived progression of pathologic changes, revolving about death of the glandular cells at the junction of glands and foveolae. Necrobiosis here was associated early with extrusion of masses of glandular cells into the most distal portions of the glands and thence through the foveolae to the mucosal surface. Evidence of glandular-cell regeneration accompanied necrobiosis. Exfoliation of the foveolar layer through the regions of necrobiosis led to localized erosion and more extensive surface denudation. Regeneration of the foveolar layer occurred quickly and was accompanied by a degree of interstitial cellular infiltration. With restoration of surface integrity, the mucosa histologically returned to normal. All tissue taken at ninety-two hours and thereafter was normal. Palmer concluded that the sudden severe damage secondary to acute staphylococcal food poisoning produces no permanent morphologic abnormality in the gastric mucosa.

Vaughan, Gunter and Erwin[118] correlated roentgenologic, gastroscopic, pathological and clinical findings in 41 cases of markedly enlarged gastric rugae. Chronic and recurring indigestion, usually aggravated by food, was present in 27 patients; the remaining 14 had ulcer-like symptoms. Fractional gastric analysis (histamine) showed an absence of free hydrochloric acid in 12 cases. Gastric resection was done for repeated massive hemorrhage in 1 patient and for chronic indigestion that had not been relieved by a medical regimen in 3. Pathological studies were done on 8 patients; all showed a chronic gastritis. The x-ray findings were characterized by chronic enlargement of the mucosal folds and irregular and sluggish peristalsis, with limited motility of the gastric mucosa. Gastroscopy was helpful in the differential diagnosis, as well as in determining the extent of the disease and prognosis. Chronic enlargement of the gastric rugae is indicative of either a chronic gastritis or neoplastic infiltration.

Lunghead and Golding[119] made a gastroscopic study of the gastric mucosa in acute infectious hepatitis, observing hypertrophic gastritis in 9 of 19 cases. It was mild in 8 and moderately severe in 1. Excess spasm of the stomach was noted in 6 cases. The authors considered these findings to offer an explanation of the gastrointestinal symp-

toms associated with infectious hepatitis. Further studies are needed to evaluate the gastric mucosa in acute and posthepatic states.

Benign Tumor

Yarnis, Marshak and Friedman[120] presented 73 cases of gastric adenomas, in 42 of which adenomas were found in a series of 2500 gastroscopic examinations. Bleeding was a significant symptom. Achlorhydria was found in 50 of 55 patients tested, and an atrophic mucosa was seen by gastroscopy in 38 of 42 patients. In no case was adenoma associated with hypertrophic gastritis. Thirty adenomas were found in 8735 autopsies. Malignant transformation was present in 2, or 6.7 per cent.

Gastric Polyps and Carcinoma

Edwards and Brown[121] state that there is much disagreement in the literature concerning malignant degeneration in benign gastric polyps. They have observed 32 patients with gastric polyps at the Cleveland Clinic in the past ten years. Seventeen had adenomatous polyps; 10 had connective-tissue polyps, and 5 had carcinoma associated with benign gastric polyps. In 2 cases in the last group the carcinoma was still in situ in a benign polyp; in 1 case there was early invasion adjacent to typical adenomatous glands. Two gastric carcinomas developed in a sixth patient eight years after excision of a benign polyp. These cases indicate that malignant degeneration does occur in benign gastric polyps. The majority of gastric polyps are asymptomatic or are associated with vague, nondescript epigastric distress. A few patients may have obstructive symptoms. Bleeding from the upper gastrointestinal tract frequently accompanies connective-tissue tumors. Hypochromic anemia is generally (and pernicious anemia possibly) associated with benign gastric polyps. Achlorhydria is also commonly observed. The diagnosis depends on both roentgenologic and gastroscopic examinations, one supplementing the other. Until more adequate follow-up studies are reported in which benign gastric polyps that were not removed did not subsequently become malignant during a period of at least twenty years, the authors believe that all benign gastric polyps should be surgically excised because of the possibility of malignant degeneration.

Klein and Geller[122] report a case in which three identical adenomas were seen gastroscopically. Two years later, two of them were found unchanged, but at the third site there was a well defined adenocarcinoma. Both the benign and malignant natures of the lesions were demonstrated microscopically. This is, therefore, apparently the first case to be reported in which a benign polyp was directly observed to undergo malignant change.

Sarcoma

Marshall and Meissner[123] state that the ratio of gastric sarcoma to carcinoma is 1:28. Diagnosis is aided by the roentgenogram and the gastroscope, as well as by frozen section at the time of operation. Treatment is radical surgical removal followed by deep irradiation when the tumor is one arising in the lymphoid tissue. The survival rate is better than that of gastric carcinoma. The five-year survival rate for leiomyosarcoma was 67 per cent, and that for tumors developing from lymphoid tissue 44 per cent.

Palmer[124] reviewed gross pathological and gastroscopic manifestations of sarcomas of the stomach. He believes that biopsies taken with the help of the flexible gastroscope, and probably cytologic study of gastric content, can be expected to improve results in the future, not only in distinguishing the sarcomas from other stomach lesions but also in differentiating the histologic types of sarcoma.

Lymphoma

Morris[125] has given a review of the literature on gastric Hodgkin's disease. Since he states that the diagnosis of Hodgkin's disease of the stomach is difficult and is usually not made before operation or autopsy, it should be emphasized that gastroscopic biopsy is a positive method of differentiating gastritis, infiltrating carcinoma and lymphoma. Although there are about 200 biopsy gastroscopes in general use, and favorable reports have been published by Shallenberger,[106] Wirts[108] and Wiebenga,[126] as well as by Benedict,[41, 105] there seems to be too little recognition of the fact that gastroscopy has at last come into its own with the other endoscopies by permitting an exact gastric diagnosis by gastroscopic biopsy under direct vision.

Peritoneoscopy

Anderson, Dockerty and Waugh[127] evaluate 396 peritoneoscopies. Fatal accidents of peritoneoscopy were not frequent, and only 1 death in their series of 392 patients could be attributed to this cause. On the other hand, a relatively large number of patients (81.2 per cent in their series) died in the hospital after peritoneoscopy. These deaths in the majority of cases, however, were attributed to the natural course of the serious diseases present or to some other procedure. It is significant that the mortality rate after peritoneoscopy was similar to that after simple trocar paracentesis performed for the same conditions. The removal of a specimen of tissue for pathological examination measurably improved the diagnostic accuracy of peritoneoscopy. The authors believed that the prothrombin level of the blood of the patient should be near normal limits if a biopsy is to be performed on the liver. Pentothal sodium, supplemented with oxygen by mask and occasionally with nitrous oxide, was employed as the anesthetic agent in more than 98 per cent of 322 peritoneoscopic examinations performed with the patient under general

anesthesia. The use of this agent did not cause an increase in mortality. It made the procedure less unpleasant for the patient and facilitated the examination. Provided there are no contraindications, any patient with a doubtful diagnosis who has ascites should be examined at least once by peritoneoscopy. This should be done to establish definitely the diagnosis in the hope that benign disease that is amenable to treatment may be found.

Benedict[41] states that peritoneoscopy may be indicated in any abdominal or pelvic condition in which the diagnosis is obscure or additional evidence is needed to confirm a diagnosis or to plan treatment. The procedure frequently gives information that will decide for or against laparotomy. In about 37 per cent of cases laparotomy is avoided by the use of the peritoneoscope. Benedict has found peritoneoscopy useful in hepatomegaly, cancer, cirrhosis of the liver, tuberculous peritonitis, unexplained ascites, pelvic tumors, ectopic pregnancy and sometimes in cases of ovarian dysfunction. In the selection of cases for peritoneoscopy it must be borne in mind that the view is limited to peritoneal surfaces and that organs or masses that are deeply situated may be seen only in certain aspects or may be impossible to visualize. In a series of 914 peritoneoscopies there have been 5 deaths, a mortality of about 0.5 per cent, (According to Ruddock,[128] only 3 deaths occurred in his series of 2500 cases, or 0.0012 per cent). Peritoneoscopy should be undertaken with an express purpose in mind — for example, to confirm a clinical diagnosis, to exclude metastatic cancer, to inspect an abdominal mass, to examine and biopsy the liver or to determine the cause of ascites. When this purpose has been successfully accomplished the case may be grouped under "purpose fulfilled." Such examinations may be positive or negative, but in all cases in this group helpful information was given to the internist in the management of the patient or to the surgeon in his decision for or against further operative procedures. In Benedict's series the purpose of the examination was fulfilled in 93 per cent of the cases.

Needle Biopsy

Since needle biopsy of the liver has in many cases replaced peritoneoscopy, it is appropriate to mention that according to Hoffbauer[129] a total of 12 deaths have been ascribed to needle biopsy in the literature reviewed. The mortality has been described as being 0.5 per cent to 0.67 per cent. Being able to see the liver at the time of peritoneoscopy is a definite advantage. It enables the operator to select an exact site for biopsy, and thus when there is only a single nodule of metastatic cancer he can obtain a biopsy from that nodule. The color, size, configuration and general appearance of the liver can be observed by peritoneoscopy. The pneumoperitoneum used during peritoneoscopy may have an inhibiting effect on hemorrhage.

Hoffbauer[129] states that unless the liver is enlarged, the lower and more anteriorly one inserts the biopsy needle, the greater the risk of entering the gall bladder. This is an unfortunate but nevertheless occasional occurrence. The principal danger inherent in needle biopsy of the liver is hemorrhage. A second hazard is bile leakage from the puncture site. Hoffbauer's experience suggests that this danger is limited to patients with high-grade extrahepatic bile-duct obstruction. Needle biopsy should not be considered a final answer to the problem of diagnosis in liver disease. It has been established as a useful and at times a decisive diagnostic adjunct; its use in properly selected cases can be recommended.

Kleitsch and Kehne[130] state that attempts to insert a needle in a small liver are dangerous because of the ease with which a loop of bowel can be perforated. The authors never do needle biopsies if the liver edge cannot be definitely palpated. A prolongation of the clotting or bleeding time should contraindicate this procedure. Another important contraindication is obstructive jaundice, the reason being that dilatation of the peripheral biliary radicles will make perforation of one of them by the aspirating needle likely. When one of these dilated biliary radicles is perforated it will tend to establish a biliary fistula, which, in turn, will produce a bile peritonitis. The authors describe such an experience, which followed needle biopsy of a patient in whom jaundice was due to carcinoma of the head of the pancreas.

Cotton and Zelman[131] report that of 18 patients with cancer subjected to needle biopsy of the liver during life, diagnosis by the biopsy was made in 9. Of the remaining patients, 6 had no liver metastases at autopsy, and the other 3 showed only small or localized metastases to that organ. I believe that the fact that small metastases may be missed by needle biopsy emphasizes the importance in such cases of visualizing the liver by peritoneoscopy and thus selecting the appropriate location for biopsy.

Warren and Drake[132] observed 6 cases of primary carcinoma of the liver in 20 consecutive autopsies carried out on patients who had had hemochromatosis. The 6 cases reported raise the incidence of hepatic carcinoma in hemochromatosis in the literature to 18.9 per cent. Peritoneoscopy would be useful in such cases.

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MEDICAL INTELLIGENCE

MONGOLISM — IMPLICATIONS OF THE DENTAL ANOMALIES*

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BOSTON

ALTHOUGH the dental defects in mongolism have not been systematically analyzed, scattered observations are recorded. Nash[1] reported that the teeth of his mongoloid patients, three to thirty-five years of age, were frequently missing, abnormally shaped or smaller than normal.[2] In a study of 3 mongoloid skulls, Greig[3] observed irregularities of the teeth that were more pronounced in the upper than in the lower jaw. In 1 skull, showing congenital absence of the nasal bones, there was a congenitally absent right upper lateral incisor (Fig. 1*A*); in the second skull the same tooth was markedly dwarfed, and the left upper lateral incisor was noted to be congenitally missing (Fig. 1*B*); and in the third skull, that of a five-year-old child with only one nasal bone, the deciduous dentition was normal (Fig. 1*C*), but no description of the successional teeth was given.

In a series of 47 mongoloid children studied at the Wrentham State School 23 (about 45 per cent) were found to have abnormalities of the permanent dentition with defects generally confined to the central and lateral maxillary incisors. Examination was performed with mirror and explorer supplemented by 41 palatal roentgenograms; anomalies were placed in three main categories according to whether teeth were congenitally missing (ablated), malformed or normal; the results are shown in Table 1. The maxillary permanent lateral incisor was the tooth most markedly and consistently affected, being abnormal in 17 (36 per cent) of the children studied. The gradient of deformity varied from absence of the tooth in 12 (25 per cent) patients through various degrees of stunting, found in 5 (10 per cent) of these mongoloid children.

The dental lamina begins its formation, first in the mandible, and a few days later in the maxilla, when the embryo is about six and a half weeks old. At seven weeks of age the buds for the deciduous central and lateral incisors are usually evident as ingrowths of oral epithelium from the primitive oral cavity (Fig. 2). As the dental primordia differentiate and penetrate into mesoderm, the cellular structure within each bud changes from flat to

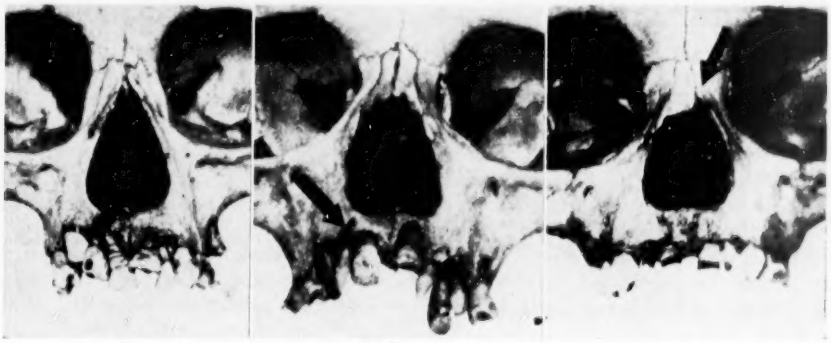

FIGURE 1. *Irregularities of Individual Teeth in Mongoloid Patients (after Greig[3]).*
A shows absence of the nasal bones and (congenital) absence of the right lateral incisor in a sixteen-year-old patient. B shows the skull of a fourteen-year-old girl; there is dwarfing and defective formation of the right and absence of the left permanent lateral incisor. C shows the skull of a five-year-old girl; only the deciduous teeth are visible, and the left nasal bone is absent.

TABLE 1. *Gradient of Defects of the Maxillary Incisors in 47 Mongoloid Children.*

PERMANENT TEETH	ABLATION NO. OF CASES	MALFORMATION NO. OF CASES	NORMAL NO. OF CASES
Central	2	2	43
Lateral	12	5	30
Canine	0	0	47

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columnar epithelium. At about eight and a half weeks of fetal age the maxillary lateral incisor buds have a wave-shaped appearance on sagittal section, marking the first step in the separation of the deciduous tooth from the undifferentiated portion of the bud from which the successional tooth will stem. According to Sicher and Tandler[4] potentialities for deciduous tooth formation lie within the "enamel knot" on the proximal aspect of the wave-shaped bud. The location of germinal centers destined to become successional teeth is not known, but injury to these cells expectedly results in agenesis, malformation or stunting of the successional tooth, or recovery without perceptible manifestations of the insult once healing has taken place.

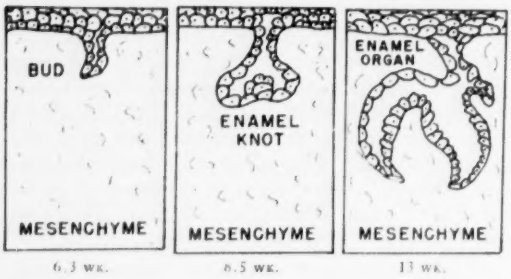

FIGURE 2. *Schematic Representation of a Lateral Incisor Tooth Bud, Enamel Knot and Enamel Organ during the Seventh, Ninth and Fourteenth Weeks of Fetal Life, Respectively.*

The fact that more than a third of these mongoloid children had congenitally missing or defective upper lateral incisors is interpreted as evidence of injury to the primordium. The inference is drawn that, just as the consequences of disease of the whole organism are death, defect and recovery without disability, the tooth or other part of the body (nasal bone or middle phalanx of the fifth finger) may suffer localized death (ablation, agenesis) or defective formation or may escape damage from disease. As an isolated finding, dental defects do not indicate the precise time when mongolism has its origin. Considered along with the dermatoglyphic, cardiac septal, occular and nasal defects, however, the findings — like the presence of Hutchinson teeth — extend definition of a syndrome that already has recognizable parts to its pattern, and a reasonable meaning to its whole design. The recognizable parts of the pattern are ablation, malformation and stunting of structures normally differentiating about the seventh, eighth or ninth week of intrauterine existence. The mongoloid baby is thought to have suffered critical stress at this period of life and to have survived — but with permanent arrest of certain ocular, dental, cardiac, skeletal and nervous tissues.

We are indebted to Drs. C. Stanley Raymond, superintendent, and Charles L. Trickey, former assistant superintendent, Wrentham State School, for administrative co-operation; and to John A. Nash, D.M.D., for his advice.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 39121

PRESENTATION OF CASE

First admission. A forty-one-year-old single caretaker entered the hospital because of a bad taste in the mouth and epigastric pain.

About fourteen months previously the patient noted the sudden onset of a "funny taste" in the mouth associated with a brown-white discoloration of the tongue and a feeling of weakness. He stopped work for two days. After this, he was well until seven months before entry, when a cold and a nonproductive cough developed. At the same time, the bad taste, which had the character of "burning rags," recurred. He also began to have nonradiating, sharp epigastric pain, which had no relation to food intake, lasted about two hours and occurred every two or three days. All these symptoms continued up to the time of admission. His appetite was poor. He felt weak and tired and had been out of work for the last seven months. He was seen at the onset by his physician, who found the blood pressure to be "over 200." Examination five months before admission revealed that the nonprotein nitrogen was 88 mg. and the hemoglobin 11.3 gm. per 100 cc. The urine contained albumin, with 2 to 4 red cells and 5 to 10 white cells per high-power field in the sediment. He had lost 25 pounds in the year before entry. He slept eleven hours every night instead of the six to seven hours required a year before admission. Nocturia (two times) occurred during the few years before entry, increasing to six times and being associated with difficulty in starting the stream for the seven months before admission.

He had had scarlet fever at the age of five. He had had a positive Wassermann test at some time in the past for which he had been treated. There was no history of hematuria, leg edema, puffiness of the face, low-back pain or headache. Bowel movements were normal. He had no known heart disease.

Physical examination showed a thin, pale and somewhat confused man. The ocular fundi were normal. The lungs were clear. The heart was not enlarged and had a normal rhythm. There was a Grade 2 systolic murmur at the apex and a split second sound at the left sternal border. The abdomen was normal. Rectal examination revealed large external hemorrhoids; the prostate was not enlarged but was slightly tender.

The temperature was 98.4°F., the pulse 80, and the respirations 18. The blood pressure was 180 systolic, 120 diastolic.

The urine had a specific gravity of 1.010 and gave a ++ test for albumin; the sediment contained 5 red cells, 50 white cells and occasional granular and red-cell casts per high-power field. Examination of the blood disclosed a hemoglobin of 11.5 gm. per 100 cc. and a white-cell count of 7400, with 66 per cent neutrophils, 30 per cent lymphocytes and 4 per cent monocytes. The red cells were of the normochromic, normocytic type. The serum nonprotein nitrogen was 170 mg., the calcium 6.4 mg., and the phosphorus 7.2 mg. per 100 cc.; the sodium was 133 milliequiv., the potassium 4.2 milliequiv., the chloride 103 milliequiv., and the carbon dioxide 18.6 milliequiv. per liter. The blood pH was 7.28. A blood Hinton test was negative. The twenty-four-hour urine sodium was 26 milliequiv. per liter. A phenolsulfonephthalein test showed less than 20 per cent excretion in two hours. A stool guaiac test was negative. A urine culture grew rare colonies of *Staphylococcus albus*. The spinal fluid was normal, with a negative serologic test. An electrocardiogram revealed a normal sinus rhythm, a PR interval of 0.12 to 0.13 second, a QRS interval of 0.08 second, a QT interval of 0.44 second and a normal axis. The T waves were inverted in Leads 1, 2, 3, V_5 and V_6, low and upright in Leads AVR and AVL, diphasic in Leads AVF and V_4 and tall and peaked, with slightly elevated ST segments, in Leads V_1, V_2 and V_3. A roentgenogram of the chest showed clear lung fields; the heart was not enlarged, but the contour of the left ventricle appeared prominent and there was a suggestion of enlargement of the left atrium. A plain film of the abdomen demonstrated kidney shadows that were normal in size and shape; there were no opaque calculi in the abdomen.

In the hospital a sore throat developed, with edema of the uvula; throat culture grew abundant alpha-hemolytic streptococci, *Staph. albus* and a few colonies of *Staph. aureus* and diphtheroids. This was treated with crystacillin and cleared after two days. The patient was treated with a diet of 60 gm. of protein without added salt, gelucil, sodium bicarbonate and Amphojel. He was discharged two weeks later with only slight improvement, the nonprotein nitrogen being 150 mg. per 100 cc. at that time. The highest urine specific gravity was 1.010, and all specimens showed ++ to +++ tests for

albumin; most sediments contained 2 to 3 red cells, 5 white cells and occasional granular casts per high-power field.

Final admission (three months later). One and a half months after discharge, the patient began to have leg edema, and was again referred to this hospital, where he was followed in the out-patient clinic. There was no dyspnea or chest pain. Examination revealed distended neck veins, a liver edge palpable 2 fingerbreadths below the costal margin and +++ edema of the legs. The patient was digitalized. About ten days later, a sharp pain developed in the right groin and testicle, which became swollen. The white-cell count was normal. A biopsy of the right epididymis was performed one week later, pathological examination of which revealed chronic inflammation and fibrosis. At about the same time, a cystoscopy showed a moderately trabeculated bladder mucosa; bladder capacity was 350 cc., and sensation was normal. A retrograde pyelogram demonstrated good filling of the left renal pelvis, calyxes and ureter; on the right side there were fewer calyxes, considered to be possibly due to a double pelvis or to a cyst in the upper pole. The intravenous indigo carmine appeared in dilute concentration in three minutes from the right kidney; there was none from the left. The patient was followed in the clinic and complained of feeling dizzy and sleepy at times; his legs went to sleep frequently, and the bad taste persisted. The day before admission he began to have sharp pain in the precordium and both shoulders. When he was examined in the Emergency Ward, a convulsion lasting five to ten minutes occurred and was followed by a postictal coma.

On physical examination the patient was semistuporous but responded to questioning. The respirations were deep at a rate of 8 per minute. The neck veins were prominent and pulsating. The lungs were clear except for rhonchi. There was a loud to-and-fro friction rub all over the precordium. The liver and spleen were not palpable. There was no peripheral edema.

The temperature was 97.4°F., the pulse 85, and the respirations 8. The blood pressure was 140 systolic, 90 diastolic.

The urine had a specific gravity of 1.010 and gave a ++ test for albumin; the sediment contained 8 to 12 white cells, occasional red cells and rare hyaline casts per high-power field. The blood hemoglobin was 10.5 gm. per 100 cc., and the white-cell count 29,700. The blood nonprotein nitrogen was 240 mg., the total protein 7.4 gm., the albumin 4.5 gm., the globulin 2.9 gm., the calcium 4.6 mg., the phosphorus 13.2 mg., and the alkaline phosphatase 2.7 units per 100 cc.; the sodium was 131 milliequiv., the chloride 96 milliequiv., the potassium 4.5 milliequiv., and the carbon dioxide 10 milliequiv. per liter. The pH was 7.12. The urine culture revealed abundant colonies of *Bacillus pyocyaneus* (*Pseudomonas aeruginosa*) overgrowing nonhemolytic streptococci. A roentgenogram of the chest showed that the lungs were clear, but the heart was larger than it had been on the previous examination.

The patient was treated with calcium gluconate, sodium lactate and fluid intravenously, but he remained drowsy and stuporous. On the fifth day, he suddenly had two generalized convulsions and died shortly after the second attack.

Differential Diagnosis

Dr. Charles H. DuToit*: May I see the x-ray film first?

Dr. Stanley M. Wyman: The original films of the chest show enlargement in the region of the left ventricle and a rather tortuous aorta. The questionable prominence of the left atrium as seen here, I think, is minimal and may be nonexistent. The lungs themselves are not remarkable. The retrograde pyelogram demonstrates slight widening of the ureters and perhaps a little blunting of the calyxes although this is very minimal. The question of a cyst in the upper pole of the right kidney is difficult to substantiate from the films. The calyxes are not as well filled on the right side, and I should go no further than that. I cannot visualize the kidneys themselves sufficiently well to say whether they are normal in size and shape; the calyceal systems of the kidneys, however, seem smaller than usual if anything rather than enlarged.

Dr. Walter Bauer: You have no films that give one a better idea of the size of the kidneys than these?

Dr. Wyman: No; I went through the whole set of films and could find none that outlined the kidneys adequately. There was so much material in the bowel, the patient being obviously very sick from the beginning, that he could not be well prepared for the examination.

Dr. DuToit: In summary this relatively young man, forty-one years of age, had symptoms possibly for fourteen months but definitely for seven months, at which time he was discovered to have hypertension and enough renal insufficiency to cause a considerable degree of azotemia. The disease then led to death in uremia about ten or eleven months after the condition was first discovered. I do not believe that anything in the clinical course subsequent to his admission to the hospital represents more than the signs, symptoms and complications of uremia itself.

Looking for clues to the diagnosis of the disease that caused the ultimate kidney failure, I am impressed by the fact that early in the history of the illness signs suggesting mechanical difficulty in the lower urinary tract appeared. Whether this difficulty in voiding was present at the onset of the disease or whether it came on subsequently is hard

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to decide. The decision depends on how much weight one places on the story that urinary frequency up to two times a night had been present for several years and on the transient episode fourteen months before admission. At any rate, close to the onset of the symptoms, it was noted that he had considerable difficulty in starting the stream and marked increase of nocturia. Apparently, the symptoms of lower-urinary-tract obstruction impressed the service because cystoscopic examination and retrograde pyelograms were performed in a critically ill patient.

I think I have to consider strongly some type of lower-urinary-tract obstruction predisposing to pyelonephritis, which itself can lead to hypertension and can impair renal function further through the development of the changes of nephrosclerosis. I cannot attribute the picture to back pressure alone—there was no evidence of a hydroureter or any degree of hydronephrosis. However, I think it is well established, even by animal experiments, that if the dynamics of urination are altered the kidneys are likely to develop infection. It is true that one cannot make a good case for kidney infection from the character of the urinary sediment. On all but one examination the number of white cells found was not too impressive. Of course, during the last admission after the cystoscopy, a high white-cell count and a considerable number of bacteria were noted in the urine; this, however, can only be positively interpreted as showing a recent acute renal infection. It does not help with the diagnosis of the earlier condition. It is well known that chronic pyelonephritis, after it has persisted for a certain period, will give relatively little evidence of an inflammatory lesion in the urinary sediment. The signs of infection such as an increase in the number of white cells and definite organisms are not consistently present in chronic pyelonephritis.

One question that I have to answer is, What type of mechanical difficulty at the bladder neck or below would be logical in a forty-year-old man? Such a lesion would have to be of a type that would not be apparent on cystoscopic examination. Such conditions as ulcers and tumors of the bladder would probably have been seen at the time the examination was carried out. A patient of forty-one is rather old for the congenital causes of obstruction such as congenital valves of the urethra and rather young for the usual causes such as benign hypertrophy and carcinoma of the prostate. I do not think the positive Wassermann test had much bearing on the case. There was no evidence from the spinal-fluid examination to suggest tabetic bladder and the cystoscopy did not suggest such a possibility.

I should consider most prominently two things, a stricture of the urethra, or a lesion in the median-bar region of the prostate. With stricture of the urethra one would expect a longer history, and it would have been detected at the time the manipulation of the urethra was carried out. This leaves as the only possibility a lesion in the median-bar region of the prostate, which tends to occur in older persons but is by no means unusual at this age. I believe some pathologists argue about its relation to other forms of benign hypertrophy of the prostate. I think in some cases inflammatory lesions have been suspected as underlying the development of such a lesion in this anatomic region of the bladder neck. Nothing suggested carcinoma of the prostate. I should expect that with carcinoma more would have been noted on rectal examination. The films show nothing abnormal in the spine or pelvis. There is no report of an acid phosphatase level.

The epididymitis that developed in the course of this disease is not an infrequent complication of mechanical difficulty at the bladder neck. Also, one might speculate about the relation of this type of lesion to past or present infection in the prostate and seminal vesicles. The possibility should be mentioned that the symptoms in the lower urinary tract were subsequent to primary disease of the kidneys, tuberculosis being the disease that comes to mind. It seems to me that there is relatively little else to suggest tuberculosis, which, because it destroys the anatomy of the kidney, would look quite different in the pyelogram. Also, one would expect different findings on cystoscopy than those reported. I might disregard the mechanical problem altogether by simply saying that it was an incidental finding or perhaps arose through increase in the daily urine volume, but I think that would be a flimsy explanation.

That brings the discussion to chronic glomerulonephritis, which is suggested by several features of the case. One is the possible exacerbating effect of upper respiratory infections, which were described on two occasions. It would be most helpful if I knew the size of the kidneys, for if they were markedly contracted I should favor a diagnosis of chronic glomerulonephritis. The notation that on one occasion red-cell casts were found in the urine is quite interesting; red-cell casts generally imply a lesion high in the nephron and are much more characteristic of acute nephritis or other diseases involving the glomerular tufts than of pyelonephritis or pressure nephrosis.

The question will come up, too, whether this could have been the end result of hypertensive heart disease alone. However, the heart was not greatly enlarged when the patient was first seen, and there were no eye-ground changes so that I may assume that severe hypertension had not been present very long.

I might mention other rare kidney diseases such as polyarteritis nodosa. Polyarteritis nodosa not infrequently causes infarcts of the testicle that may also appear to involve the epididymis. I do not think I am justified in carrying this possibility

too far in the absence of other symptoms suggesting this diagnosis.

Other conditions such as amyloid disease I do not think have to be seriously considered. There is not enough to go on except for the x-ray report of one questionable cyst to make a diagnosis of polycystic kidneys. The kidneys were not palpable; there was nothing in the other kidney that suggested polycystic disease.

I have not related the abdominal pain to the kidney disease. I cannot think of a good explanation for the pain. It seems to have been too persistent to be explained by the gastritis of uremia. The enteric involvement that one sees in the mucosa of the stomach and intestines in uremia is usually a terminal affair of relatively short duration. I wonder whether it could have represented the development of infection in the kidney. I do not know how else to bring it in.

I shall give as my first diagnosis chronic pyelonephritis with a certain amount of nephrosclerotic change. I should expect that the patient had a median-bar hypertrophy of the prostate and that terminally he had some superimposed acute pyelonephritis. My second choice is chronic glomerulonephritis. I shall throw in the possibility of a peptic ulcer or some other lesion to explain the epigastric pain.

Dr. Bauer: May we have the history that pertains to familial disease?

Dr. Benjamin Castleman: The patient's father is alive, is seventy-seven years old and has heart trouble. Two brothers died of a heart attack at the ages of twenty-two and forty-two; 2 others are living and well.

Dr. Wyman: Dr. DuToit, do you think the change in the calyceal system of the kidneys was minimal if the patient had severe chronic pyelonephritis? Is this not more in keeping with glomerulonephritis?

Dr. DuToit: I think it is possible for minimal lower-urinary-tract obstruction to damage the kidney by predisposing it to repeated infection.

Dr. Bauer: Do you think the patient had so much trouble with the bladder at the ureterovesical junction?

Dr. DuToit: He had a trabeculated bladder, not enough alone to cause renal damage but perhaps enough to predispose the patient to infection.

Dr. Bauer: Did he have polycystic disease of the kidney? He died at the age of forty-one.

Dr. Alexander Leaf: Those of us who followed this patient in the renal clinic were not so much impressed with the evidence for urinary-tract obstruction. Our impression was that this was most probably chronic glomerulonephritis though the difficulties of distinguishing between chronic glomerulonephritis and pyelonephritis at this stage are well appreciated. The reason for the pyelogram was that the epididymitis that developed on examination seemed most consistent with infectious epididymitis perhaps tuberculous in origin. There was also in favor of tuberculosis the fact that the patient worked in a tuberculosis sanatorium for a number of years. The retrograde pyelogram was to rule out the possibility of tuberculous disease of the kidney.

Dr. Farahe Maloof: When the patient was on the service, our diagnosis was chronic renal disease with uremia. The question arose at that time whether pyelography or cystoscopy should be done. We finally decided not to do anything in view of the potential hazards from these procedures in this sort of patient especially since we thought that nothing could be gained.

Clinical Diagnoses

Chronic glomerulonephritis.
Uremic pericarditis.
Chronic pyelonephritis.
?Double renal pelvis, right.

Dr. Charles H. DuToit's Diagnoses

Chronic pyelonephritis, with nephrosclerosis.
Median-bar prostate hypertrophy.
Acute pyelonephritis.
?Chronic glomerulonephritis.

Anatomical Diagnoses

Acute and chronic pyelonephritis.
Pericarditis, uremic.
Pulmonary edema, severe.
Bone-marrow embolism of lung.

Pathological Discussion

Dr. Castleman: At the time of autopsy we found an enlarged heart — it weighed 600 gm. — and a pericarditis of the uremic type with 200 cc. of fluid and fibrin in the pericardial cavity. The lungs showed severe edema and no pneumonia. The kidneys were about half the normal size, weighing 180 gm., and were uniform and coarsely granular. The external appearance was that seen in chronic glomerulonephritis except for one finding that did not fit: numerous small cysts scattered over the surface between which a good deal of renal tissue still remained. When the kidneys were cut, many of the cysts were fairly large, one measuring up to 2 cm. in diameter on the right. These cysts as a rule are not seen in a chronic glomerulonephritis. The renal markings were almost completely obliterated. The ureters were not dilated, and the bladder appeared to be merely congested. There was no median-bar lesion and no enlargement of the prostate. The right epididymis was a little scarred, but there was no evidence of an acute infection; the testes were normal.

The microscopical sections of the kidneys showed a clear-cut pyelonephritis; there was no glomerulonephritis. The pyelonephritis was both old and

recent. There were polymorphonuclear neutrophils and colloid casts in the tubules, necrosis of the tubular epithelium and acute and chronic changes in the tufts, the acute changes being of the type that is seen with a pyelonephritis. The interstitial tissue was densely infiltrated with polymorphonuclear leukocytes and lymphocytes and there was a large amount of scar tissue as well. We have no explanation for the etiology of this pyelonephritis. It involved both sides equally, and I believe there

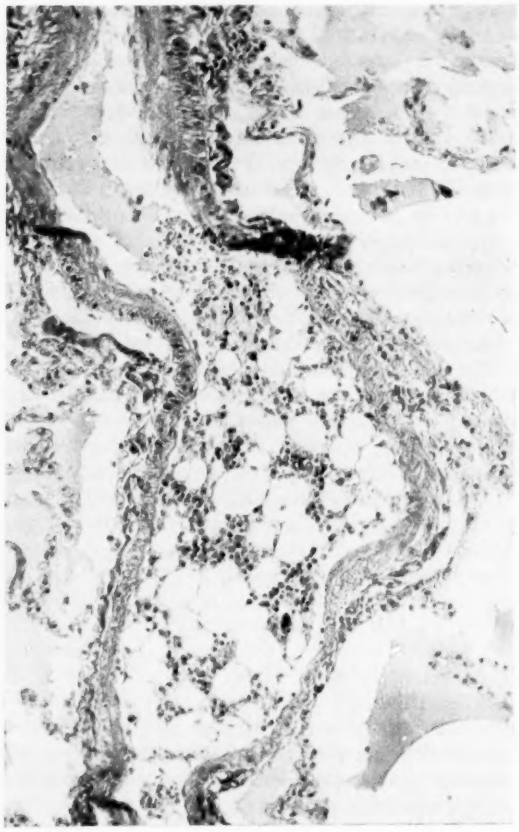

FIGURE 1.

was a blood-stream infection in the past. The vascular changes in the kidney were quite prominent, but no evidence of polyarteritis was noted. The cysts were probably the result rather than the cause of the pyelonephritis. They did not appear to be the type seen in congenital cystic disease.

An incidental finding in the lungs was of great interest. The pulmonary arteries contained bone-marrow emboli composed of fat and myeloid cells (Fig. 1). This is not fat embolism; it is actually the bone marrow itself acting as an embolus. The cause of bone-marrow embolism is almost always a bone fracture and usually a major fracture; but often there is no evidence of a definite fracture, and Rappaport et al.* believe that violent muscular contractions, such as may occur with a convulsion, may so injure a vertebra that cancellous bone marrow may be forced into the contiguous sinusoidal veins, becoming emboli. Bone-marrow embolism has also been observed in the lungs of patients who have had convulsions associated with tetanus and shock treatment in whom there was no evidence of an injury grossly. This patient had two severe convulsions just before death, and the bone marrow looked quite viable so that the emboli were not present more than a few hours. I do not believe they had anything to do with the cause of death although in a few reported cases they have extensively involved the lungs; in the absence of another cause, death has been attributed to these bone-marrow emboli.

*Rappaport, H., Raum, M., and Harrell, J. B. Bone-marrow embolism. *Am. J. Path.* **27**:407-433, 1951.

CASE 39122

PRESENTATION OF CASE

A fifty-eight-year-old housewife was referred to this hospital because of pain in the neck.

Six weeks before admission the patient noted soreness and stiffness of the anterior portion of the right side of the neck but paid little attention to it. Two weeks later the left side became sore and swollen, and there was slight discomfort about the left ear. She was very lethargic and had a chilly sensation without actual shaking at night. Her physician found an enlarged thyroid gland and a temperature of 99.6°F. She was put to bed for a week and treated with aureomycin for four days, without improvement.

At no time had she noted excessive sweating or nervousness. She had lost 8 pounds during the present illness. The past history and systemic review were otherwise negative.

Physical examination revealed a well developed and well nourished woman. The thyroid gland was movable and diffusely enlarged bilaterally. The left lobe was tender; there was no bruit. The heart and lungs were normal except for a tachycardia. The liver and spleen were palpable at the costal margins and were not tender. The rest of the examination was negative.

The temperature was 98.6°F., the pulse 100, and the respirations 20. The blood pressure was 135 systolic, 80 diastolic.

The urine had a specific gravity of 1.026 and gave a + test for albumin; the sediment contained 12 white cells and a rare hyaline cast per high-power field. Examination of the blood showed a hemoglobin of 13.4 gm. per 100 cc. and a white-cell count of 8800, with 72 per cent neutrophils, 23 per cent

lymphocytes and 5 per cent monocytes. The sedimentation rate was 47 mm. in sixty minutes. The basal metabolic rate was plus 8 per cent. The radioactive-iodine uptake was 0 per cent in forty-eight hours; the protein-bound iodine was 10.6 microgm. per 100 cc.

On the second hospital day an operation was performed.

Differential Diagnosis

Dr. William C. Quinby, Jr.*: It appears to me that anyone reading this protocol cannot fail to be impressed with the inflammatory nature of the disease affecting this patient. Also, it is obvious that this disease did not run an acute suppurative course nor a very prolonged and chronic one. Therefore, the presumptive diagnosis of a subacute, nonsuppurative, inflammatory disease affecting the thyroid gland is tenable on clinical grounds alone. The findings of the clinical laboratory and the special tests of thyroid activity serve to exclude many of the commoner forms of goiter and to cast doubt upon most forms of cancer of the thyroid gland. At the same time they support the impression gained from the history, clinical course and clinical findings to such a degree that the entire protocol becomes a so-called classic picture. I must review this for a moment.

The patient was a woman fifty-eight years of age. Most patients exhibiting thyroiditis are women, and most are between thirty-five and sixty years of age. One slight imperfection is that no known systemic or upper respiratory illness existed before she noted soreness and stiffness of the neck. Some such illness often antedates the onset of thyroiditis, so that a virus or bacterium has been favored as the initial cause for the disease. Her physician may have been thinking along the same lines, for when faced with low-grade fever, chilliness, lethargy and an enlarged and tender thyroid gland, he gave the patient aureomycin. His impression must not be taken lightly, for he saw her at a time when her illness apparently was more acute, and his treatment indicates that he thought she had thyroiditis.

When referred to this hospital she complained of pain in the neck. She gave no history or evidence on physical examination that would indicate thyrotoxicosis or myxedema. I have no evidence that a goiter existed before this illness. She showed a fast pulse and a high sedimentation rate and a high normal white-cell count, none of which are diagnostic of any specific thyroid disease but all of which customarily occur in subacute thyroiditis. The protocol does not mention vocal-cord paralysis, difficulty with respiration, inability to extend the neck without pain, presence or absence of lymph-node enlargement in the vicinity or any distinguishing consistence of the thyroid gland. I cannot count on this absent information, but when it is coupled with the duration and course of the disease, I am justified in excluding acute inflammation or abscess and probably in excluding the chronic forms of thyroiditis called Riedel's and Hashimoto's struma. Rapidly spreading cancer of the small, round-cell type cannot be excluded, but other forms probably can since this was a diffuse disease. A hemorrhage or degeneration of some pre-existing diffuse nodular disease of the gland also seems unlikely.

I am interested in the symptom of discomfort about the left ear, mentioned toward the beginning. This is frequently cited in the literature about the acute or subacute forms of thyroid inflammation. I have tried to find an explanation for it since I do not remember this symptom in postoperative patients or in those who had extensive cancer. If the symptom applies to the external ear, it can easily travel along the sensory pathways of the second and third cervical nerves, which give rise to the greater auricular nerve as well as to the cervical branches supplying the skin of the neck anteriorly. This is a reasonable explanation, since pain in the occipital region or down the arm posteriorly also occurs in thyroid inflammation and could follow a similar reflex path. Pain referred to the eustachian orifice or inner parts of the ear is harder to explain, but might originate in the superior laryngeal nerve and travel with the vagus. However it may be, the symptom operates here to support the impression of thyroiditis.

Turning to the tests for thyroid activity, I find a dramatically low uptake of radioactive iodine. This practically excludes the existence of any functioning thyroid tissue. If functioning tissue did remain, it must have been saturated with iodine before the test, and hence incapable of assimilating any more. There is no evidence that this occurred. Even extensive involvement with cancer does not usually eliminate iodine uptake to this degree, whereas patients with lymphadenoid (Hashimoto's) struma show an average of 20 per cent uptake. The evidence against pre-existing colloid cysts or adenomas is similarly supported by this finding. True myxedema is also unlikely in the presence of a protein-bound iodine level of 10 microgm. per 100 cc., which is definitely an elevated value. Again, this is not likely in cancer but is characteristic of thyroiditis, in which it is thought that the inflammation may rapidly displace thyroid hormone (or the form of it that is measured as protein-bound iodine) from the gland. One school believes that the subacute form of thyroiditis (pseudotuberculous, granulomatous, giant-cell, DeQuervain's) may represent an inflammatory reaction to the colloid formed by the gland itself — as though the colloid suddenly becomes venomous and destroys secreting cells, the débris being cleaned up by giant cells and other phagocytes.

*Assistant in surgery, Massachusetts General Hospital.

Characteristically, the end-organ effect of thyroid hormone, the basal metabolism, was normal in this patient. This does not help me in diagnosis. I can only say that until thyroiditis has completely destroyed all thyroid tissue, myxedema is not encountered, and in this case the six-week interval was not long enough for the basal metabolic rate to tell us anything. For the same reason it does not help to exclude cancer.

There is some disagreement in the literature about the eventual course of subacute thyroiditis. Crile[1] believes that it subsides, leaving slight residual disorders of function. Others[2] say that it may progress to tracheal compression and a picture that is easily confused with Riedel's ligneous thyroiditis. Riedel's struma, in turn, may represent a degenerating nodule, as evidenced by its unilateral nature and the presence of adenomatous tissue in the center of the dense scarring. The entire nature of thyroiditis is confusing and still in the stage of clinical and microscopical description.

In summary, the age and sex of the patient, the relatively short but progressive nature of the disease, the pain in the ear, the initial low-grade fever, the chilliness, lethargy and slight weight loss, the fast pulse, the elevated sedimentation rate, the migratory nature of symptoms from right to left thyroid lobes, the diffuse enlargement with tenderness over the left lobe, the absence of tracheal fixation and the absent radioactive-iodine uptake, with elevated protein-bound iodine and normal basal metabolic rate, form a characteristic picture.

One may ask, Why operate if this disease is so characteristic and may subside without serious sequel? I believe that in spite of all the clinical and statistical logic that we can muster, this woman had to have an exploratory operation to make the diagnosis certain and to meet and treat cancer if the reasoning was found to be false.

Dr. Winfield S. Morgan: Dr. Quinby has analyzed this case very well; however, the operation was not exploratory in the sense in which we usually use the term. Dr. Hamlin, would you care to comment about the operation?

Dr. Edward Hamlin, Jr.: The operation was a needle biopsy of the left lobe of the thyroid gland with a little novocain infiltration. A Vim-Silverman needle was introduced into the substance of the thyroid tissue and a small core removed. This procedure was a little more uncomfortable than it usually is, because of the tenderness of the thyroid gland.

Dr. Earle M. Chapman: We agreed entirely with Dr. Quinby's interpretation. I think the swinging temperature to 101 and 102°F. together with the local signs, convinced her physician in Maine, who was not familiar with this pattern of thyroiditis, that bacterial infection was present.

Clinical Diagnosis

Subacute thyroiditis.

Dr. William C. Quinby, Jr.'s, Diagnosis

Subacute thyroiditis.

Anatomical Diagnosis

Subacute thyroiditis, giant-cell type.

Pathological Discussion

Dr. Morgan: The specimen we received in the laboratory was a thin cylinder of tissue measuring about 2.0 cm. long and 0.2 cm. in diameter. Microscopically, this showed a characteristic picture of subacute or giant-cell thyroiditis (Fig. 1). There was extensive fibrosis, loss of acinar parenchyma and a diffuse, moderate infiltration by polymorphonuclear neutrophils, lymphocytes and eosino-

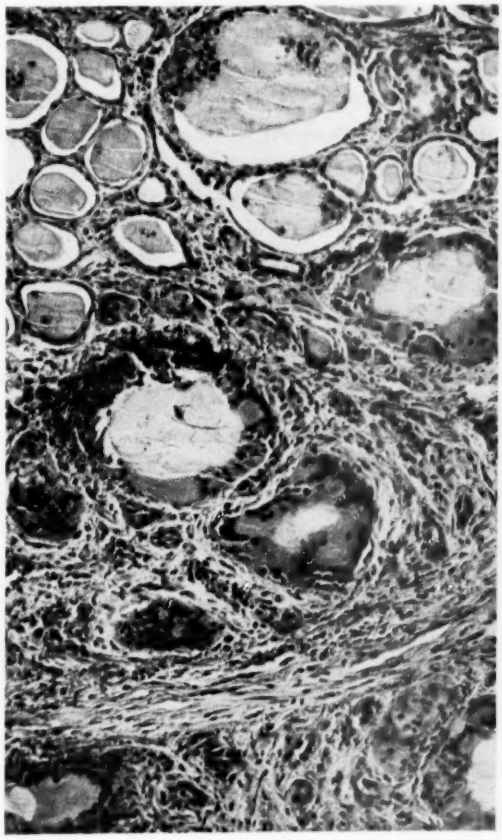

Figure 1.

phils. Focal abscesses were present in places. In addition, there were granulomatous lesions composed of epithelioid cells and multinucleated giant cells surrounding masses of colloid. The thyroid acini that persisted had low epithelium and contained small amounts of colloid and occasionally cellular débris.

Many terms, such as subacute, giant-cell, pseudotuberculous and granulomatous thyroiditis, have been used to describe this condition. Its etiology is unknown, but the possibility of its being caused by a virus has been proposed by some writers although to my knowledge there have been no reports of its occurring in epidemic form. Crile[3] believes that it is to be differentiated from Riedel's struma by the fact that in subacute thyroiditis the inflammation or scarring is limited to the thyroid gland whereas in Riedel's struma there is extension to surrounding structures. It seems to me that these are rather meager grounds on which to attempt to distinguish two pathologic processes. I have been unable to find a good clinical and pathological study of a significant number of cases describing histologic features by which these two conditions might be distinguished. Since in many cases of subacute thyroiditis the inflammation and fibrosis are severe and the local signs, such as tenderness and radiation of pain to the ear, are often prominent, the last strongly suggesting that there is extra-thyroid extension of the inflammation, I wonder if the element of degree of inflammation does not play a deciding role in determining which cases are to end up as "healed subacute thyroiditis" and which as "Riedel's struma." This is a confusing subject, to which the final answer does not appear to have been given. In a recently published study by Lindsay and his co-workers[2] in which 354 cases of chronic thyroiditis were reviewed, 23 cases were classified as subacute or giant-cell thyroiditis. The photomicrographs demonstrated the same lesion found in the case presented today. Yet 13 of 19 cases were described as being extensively adherent to the trachea or adjacent muscles, and with but 2 exceptions these glands were described as firm, hard or even of the consistence of wood or stone. These, of course, are the classic descriptions of Riedel's struma.

DR. CHAPMAN: It has been stated that many of these patients go into myxedema after the disease subsides spontaneously or after the dramatic improvement that is seen after external radiation therapy. The patient under discussion experienced prompt relief from x-ray treatment, and the fever ceased the day after the first x-ray dose. This reaction to x-rays is a mysterious affair. Six weeks after therapy she had regained weight and felt well again. The thyroid gland was just palpable, and although there were no signs of myxedema the uptake of radioactive iodine was only 5 per cent in forty-eight hours and the protein-bound iodine was 0.4 microgm. per 100 cc.

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GROUP PRACTICE IN A RURAL AREA

Group practice, so opposite in many ways to the purely private, individual practice of medicine, has been a natural subject of debate since it first assumed proportions that have made it conflict, at times and in places, with the activities of the independent practitioner. Particularly fruitful subjects for controversy have been such great organizations as the Health Insurance Plan of New York, known by its anatomically suggestive abbreviation of HIP, and the Permanente Foundation of California.

The *Journal*, inclined so far as possible to view both sides of any question, has been criticized for suggesting that the latter plan might be worthy of careful study. Even the toad, these critics seem to forget, despite its unprepossessing exterior, may yet contain some jewels in its low-vaulted dome.

In what it believes to be a justifiable desire to serve as an unbiased medium for the exchange of ideas the *Journal* has presented, elsewhere in this issue, a paper on "Group Practice with Branch Centers in a Rural County." This paper was read at a meeting of the American Public Health Association.

Established with the idea of solving some of the problems of rural medicine as they existed in Columbia County, New York, in the upper Hudson River valley, the organization under discussion, for geographical rather than descriptive reasons, has called itself the Rip Van Winkle Clinic. If the title has any particular reference to rural medicine the implication is that of its awakening rather than of any preliminary slumbering.

In order that the Clinic might become a factor in promoting the health of the area that it serves, adequate hospital facilities had to be provided. This was accomplished by the community itself with help furnished under the Hill-Burton Act. High-grade personnel has been attracted to the Clinic so that today it is staffed by 17 physicians, all of whom have passed or are eligible to take their American board specialty examinations, a factor that need not be considered as disqualifying them for rural practice.

Certain economic essentials of complete medical care have been provided as well, most important of which is that of supplying service at a cost that 90 per cent of the people can afford. The fees, in fact, are equivalent to those that confront the full-rate patient in the so-called free outpatient department in New York City. Nor have the medically indigent been neglected, for the dispensary of the clinic has furnished approximately $88,000 worth of free care in six and a half years.

A cancer-detection clinic has been opened and is recognized by the American College of Surgeons. Here relatively complete physical examinations have been introduced, and as an outgrowth an "annual-review" program has been instituted.

Still to be settled are the eventual relations of such a clinic with the people and the independent practitioners of the region. If its apparent success continues, however, it will have to be recognized as a challenge to the time-honored fee-for-service basis of providing medical care.

EDITOR'S UNEASY CHAIR

THE National Science Foundation, having been authorized and directed by the basic legislation that created it to encourage the dissemination of scientific information, conducted last year a survey of scientific and technical publications. Among the 205 periodicals to which questionnaires were sent and from 110 of which replies were received, were an undisclosed number of medical journals.

The general purpose of the survey was to gather information on the rapidly increasing volume and the still more rapidly rising costs of publication, which together have created almost universal financial problems. At least part of the increase in volume of scientific output that requires expression is explained by the fact that expenditures for research and development have increased from $900,000,000 in 1942 to $2,900,000,000 in 1952. The questionnaire included requests for opinions regarding possible sources of additional support to the publications, as well as the purposes for which additional funds were needed.

The rate of return of the questionnaire varied widely in different fields of scientific endeavor; thus, whereas 88 per cent of the questionnaires sent to geological journals were returned, a yield of only 35 per cent was obtained from journals of engineering. Since only 8 geological and 40 engineering journals were interrogated, however, these percentages can hardly be considered as significant. No comparable figures in regard to journals of medicine were revealed.

The circulation of the journals answering the questionnaire varied from less than 500 to more than 60,000, with an average of about 6000. Those with small circulation disclosed the not unexpected fact that less of their support came from advertisements and more from subscriptions and society contributions than is the case with the widely distributed periodicals. Advertisers are naturally interested in numbers of readers. About half the editors believed that more advertising would be the most appropriate way in which to increase their journals' revenue; these were mostly those responsible for the journals with many subscribers.

Societies and private foundations were listed as agreeable sources of increased revenue; relatively few editors were enchanted with the idea of being beholden to government, or to industry either, except through legitimate advertising. Other possible ways suggested for obtaining better revenues were higher subscription rates — which tend automatically to discourage subscribers — higher reprint charges and a page charge to be paid by author or institution sponsoring the research. Sixteen of the 110 journals already tax their authors for the privilege of publication, and 11 others charge for pages above a certain number. Twenty-six require payment for plates and tables.

Methods of putting to use a hypothetical increase in funds were also inquired into; 43 per cent of the editors would use them to increase the speed of publication, 84 per cent for additional pages and 30 per cent for the publication of longer articles, which might conceivably amount to the same thing. Fifty per cent would apply this opulence to an increase in editorial help, and 25 per cent to improved format.

A number of editors took the opportunity to complain of the "large number of articles that are badly written, repetitious, over-long, and in which the presentation of scientific material was confused even where reported results and techniques appear to be sound."

Certain yearnings seem thus to have been expressed with no ready way of satisfying them. A diagnosis may in itself afford some comfort, however, even where no immediate cure is available.

CONCERNING EMANATIONS

FROM the number and variety of deodorants that have been offered the American public in recent years, it might be surmised that this great nation, despite its addiction to the bath, is made up of a rather unsavory lot of individuals. It is reported that Orientals find them so, attributing the fact to their preference for bread and meat over fish and rice.

However this may be, Americans have certainly been made smell conscious. This condition of osmosis, in the newer, braver, commercial sense of the word (osme — Greek for bad smell, osis — Greek for pathologic state), is, according to the advertisers, easily correctible by a variety of wonder drugs. One of the newest and not the least of these is chlorophyll, sprinkled, dusted, sprayed or eaten.

Odors, it is commonly believed, result from the dispersion of tiny particles of odoriferous matter. To neutralize the lingering aroma of Liederkranz cheese or stale tobacco smoke or the penetrating odors of other, more objectionable substances, it would be necessary to find chemicals that would specifically unite with the molecules of each and neutralize or destroy them. This is manifestly impractical. The smell of ammonia might be counteracted by a spray of hydrochloric acid, but neutralizers for the complex organic molecules of all scatologic essences would be difficult if not impossible to find.

Those who are curious about the true composition of some of the newer devices for reconditioning the air of a room the morning after a late party need only send a quarter, and the United States patent number of the product about which information is desired, to the Patent Office in Washington. Specifications will be forwarded by return mail.

One of the most popular of these devices is a bottle of green liquid with a felt wick. The bottle contains a little more than 2 per cent chlorophyll, to be sure, but, as the inventor plaintively states in his plea for exclusive financial rights, "chlorophyll is relatively inactive." This inactivity is remedied by the addition of about 12.5 per cent of formalin. The fact that goats eat chlorophyll, used as a further argument against the effectiveness of this substance as a deodorant, still stands unrefuted.

The action of formaldehyde is less upon the smell than upon the smeller. A plate of 10 or 12 per cent formalin placed in an ill smelling room may be said to deodorize the chamber, because it paralyzes the sense of smell of all who enter. No smeller, no smell. Simple, and a million-dollar idea. One plugs one's ears to shut out discordant sounds; one deadens sensory nerves with novocain and is just as happy as though cacophony had been replaced with harmony or pain with — well, whatever the antonym for pain may be.

Better to air out the room? Don't be reactionary! Antosmotics work on the real source of trouble — the nose. What is more important, they keep one's money in circulation.

In Massachusetts the number of State paupers who are foreigners, is "eleven thousand, three hundred and twenty-one." — In 1852, 2,361 were sent to prison in Massachusetts, for intemperance. — The whole number of interments at Mount Auburn Cemetery, near Boston, since it was opened to the public, is 5,580.

Boston M. & S. J., *March 23, 1853*

MASSACHUSETTS MEDICAL SOCIETY

DEATH

AHEARNE — Cornelius A. Ahearne, Jr., M.D., of Marblehead, died on July 21, 1952. He was in his eighty-fifth year.

Dr. Ahearne received his degree from Harvard Medical School in 1889. He was formerly Salem city physician.

He is survived by his widow, two daughters, two grandchildren, a brother and three sisters.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The April schedule of the Consultation Clinics for Crippled Children in Massachusetts is as follows:

Orthopedic Clinic	Date	Clinic Consultant
Haverhill	April 1	William T. Green, M.D.
Greenfield	April 2	Charles L. Sturdevant, M.D.
Salem	April 6	Paul W. Hugenberger, M.D.
Gardner	April 7	Carter R. Rowe, M.D.
Brockton	April 9	George W. Van Gorder, M.D.
Lowell	April 10	Albert H. Brewster, M.D.
Lynn*	April 13	Daniel M. Killoran, M.D., and John J. Crowley, M.D.
Worcester	April 17	John W. O'Meara, M.D.
Springfield	April 21	James D. Fisher, M.D.
Hyannis	April 23	Paul L. Norton, M.D.
Fall River	April 27	David S. Grice, M.D.

Rheumatic-Fever Clinic	Dates
North Reading	April 7, 14, 21, 28
Fitchburg	April 8, 15, 22, 29

Plastic Clinic	Held	Consultant
Eastern Massachusetts	Semi-monthly	Bradford Cannon, M.D.
Western Massachusetts	Monthly	Joseph M. Baker, M.D.

Physicians referring new patients to clinic should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Hospital.

CORRESPONDENCE

LICENSING OF CHIROPRACTORS

To the Editor: On Thursday, February 26, a curious scene was enacted in the Massachusetts State House. From 10:30 in the morning, and continuing until 2:45 in the afternoon, one man after another earnestly petitioned the Public Health Committee to establish the legal right to practice chiropractic. They had come a long way in their determination, from the days when its founder, an Iowa grocer, offered a diploma after six months of tutelage. They now pointed to a four-year course covering 3600 hours of study, as compared to Johns Hopkins University School of Medicine, which requires several hundred hours' less time for the degree of Doctor of Medicine. For this 3600 hours they asked little: merely the right to thump a citizen's spine in broad daylight in the office of a Doctor of Chiropractic, rather than illegally and behind drawn shades in their houses. They promised to put the State to no expense in the establishment of a board of examiners, and there was even a hint of available revenue in their suggestion that they pay yearly licensing or registration fees up to $100.

What in this impressive 3600 hours of study did the ambitious chiropractor learn that made him unable to prescribe medicines, diagnose ailments from the common cold to the simple fracture, interpret laboratory analyses or understand the sounds a human heart makes? For, in spite of their gruelling years of study, they requested no permission to do all these things; in fact, they admitted that their one and only treatment for high blood pressure, cancer, tuberculosis, broken bones, poliomyelitis and the host of other ills that plague mankind was the same: a knowledgeable and learned thump on the spinal column.

And when these petitioners, their legal counsel and their paid lobbyist had finished speaking they called upon those who would also speak for them. In all, 8 or 9 legislators went on record in their favor, in addition to a bank president, who had sat all morning waiting to testify in their behalf, and various eloquent representatives of the Disabled Veterans and Massachusetts Grange and a "Plain Citizen" who traveled regularly to another state for chiropractic aid for his child when she had a high fever. So, for four and a quarter hours, this went on, while members of the listening committee left briefly to answer roll calls in the Senate and House chambers, and to attend to minor duties.

When the lawyer for the Massachusetts Medical Society was finally called it was 2:45. At that time only 4 members of the committee remained to listen to the medical opposition, and when the first man, a roentgenologist, began his testimony, 3 members hurried out for a roll call, leaving only 1, and remained away for the entire testimony of this doctor. Nor at any time thereafter, until adjournment at 4:30, was there an equal complement of the committee to listen, compared to the number present for the chiropractors. In the ensuing time 5 doctors spoke against the licensing, and only 2 legislators came to their support.

Did this unequal situation matter? If, according to some, the decision had already been made by the Committee before the public hearing, for what purpose was this drama enacted? Was it to encourage the proponents who had packed the chamber, leaving their businesses for the day, and bringing their families with them? Was it to underscore the eventual defeat of the opponents, whose sum total were 5 doctors and a tiny oasis of the Massachusetts Medical Auxiliary? In the corridor Senator Cutler said that it was going to be a "tight squeak — and the doctors had better get busy with telephone calls to their legislators."

Several years ago when the chiropractors and their friends had carried their bill successfully to Governor Tobin's desk for his signature, he asked, as he vetoed the bill, "Where were the doctors when this bill was under consideration?"

(Mrs. Mark F.) Helen R. Lesses
State Legislative Chairman
Massachusetts Medical Auxiliary

PHOTO FINISH

To the Editor: The column, "By the London Post," in the December 25, 1952, issue of the *Journal*, discusses the separation of the surgical profession from the barber profession. While not attempting to pique Dr. Lister, I should like to elaborate on this fascinating story. The authority for these facts come from the text, *Menders of the Maimed*, by Sir Arthur Keith.

For centuries, the surgeons and barbers had been joined in common company known as "Masters or Governors of the Mystery and Commonalty of the Barbers and Surgeons of London." The aspiration of the surgeons, led by William Cheselden, was to make a common fund of knowledge, spread the art of surgery and healing, and do away with all mystery. Dr. Lister mentioned that William Cheselden was a surgeon of wide fame who was able to perform lithotomy by the perineal route in thirty seconds. The records state that Cheselden did this operation in fifty-four seconds. It is not intended as a picayunish point, but that is really a whopping exaggeration. The local tradition saw close guarded secrets passed from father to son and from master to apprentice. To realize their ideal, the surgeons waived all rights to the monies of the old City Guild. Parliament granted their wish, and thus was formed, "The Master, Governors, and Commonalty of the Art and Science of Surgeons of London." This later became the "Royall College of Surgeons of England."

Paul R. Miller, M.D.

Columbus, Ohio

Dr. Miller's letter was submitted to Dr. Lister, whose reply is as follows:

To the Editor: It may perhaps seem a quibble to argue about how much less than a minute it took William Cheselden to perform his operation of lithotomy, but in the face of Dr. Miller's challenge, I should like to defend Mr. Zachary Cope's claim that thirty seconds (rather than fifty-four as stated by Dr. Miller) was his best time. Mr. Cope told me that I would find the evidence for the shorter time in an article by the anatomist Dr. James Douglas (of Douglas–pouch fame) at the Medical Society of London. Douglas was a great friend of Cheselden's and helped him to work out the anatomy of the operation of lithotomy. He wrote one article entitled "The History of the Lateral Operation for the Stone" and another entitled "An Appendix to the History of the Lateral Operation for the Stone, containing Mr. Cheselden's present method of performing it."

On page 16 of the latter article, he writes of Mr. Cheselden: "He performs this operation with so much dexterity and quickness, that he seldom exceeds half a minute, unless when he is obliged to take up and tie the vessels before the stone is extracted or when there happens to be something uncommon in the stone itself."

The article was printed at The Golden Ball "over against the Royal Exchange in Cornhill, London," in the year 1731, and it is thought probable that the copy at the Medical Society of London, which Mr. Cope and I have both consulted, is the only one in existence. Nevertheless, I hope that this evidence will convince any doubters, and in conclusion I can only add that as the result of his research, Mr. Cope is hoping to publish a book about William Cheselden that should make very interesting reading.

John Lister, M.D.

London

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Handbook of Cardiology for Nurses: The disease, the patient, modern concepts of treatment. By Walter Modell, M.D., assistant professor, Cornell University Medical College, and associate cardiologist, Beth Israel Hospital and Hospital for Joint Diseases. With a foreword by Edna L. Fritz, R.N., assistant professor of medical nursing, Cornell University–New York Hospital School of Nursing. 8°, cloth, 246 pp., with 3 illustrations. New York: Springer Publishing Company, Incorporated, 1952. $3.50.

This handbook presents the information necessary to nurses in caring for patients with heart disease. Emphasis is placed on the drugs used in the treatment of heart conditions, 36 pages being devoted to this subject. An appendix discusses the low-salt (sodium) diet and the sodium content of foods and water.

The Metabolic Response to Surgery. By Francis D. Moore, M.D., Moseley Professor of Surgery, Harvard Medical School, and surgeon-in-chief, Peter Bent Brigham Hospital, Boston; and Margaret R. Ball, A.B., Department of Surgery, Harvard Medical School, and Laboratory for Surgical Research, Peter Bent Brigham Hospital, Boston. With metabolic diagrams by Mildred B. Codding, M.A., surgical artist, Department of Surgery, Harvard Medical School, and Peter Bent Brigham Hospital, Boston. 4°, cloth, 156 pp., with 48 illustrations. Springfield, Illinois: Charles C Thomas, 1952. $7.50. (Publication No. 132, *American Lecture Series.*)

In this monograph the authors present the results of their studies on the metabolic response in surgical conditions in 30 cases and a survey of the relevant literature. The technic is first described, followed by chapters on response to a single trauma, consideration of starvation, immobilization and endocrine factors, trauma and depletion, complex problems in metabolic response and changing the balance. The text concludes with a summary of the facts and corollaries, numbering 23. An appendix is devoted to surgical diets and parenteral supplements. There is a bibliography of 9 large pages. The monograph should be in all collections on surgery.

A Synopsis of Neurology. By W. F. Tissington Tatlow, M.D., M.R.C.P. (Lond.), medical registrar, Maida Vale Hospital for Nervous Diseases, London; J. Amor Ardis, M.B., Ch.B., D.P.M. (Brist. & Lond.), senior registrar in psychiatry, Aberdeen General and Mental Hospitals; and J. A. R. Bickford, M.R.C.S., L.R.C.P., D.P.M. (Brist.), senior registrar in psychiatry, Maryfield Hospital, Dundee, and Dundee Mental Hospital, Gowrie House. 12°, cloth, 513 pp., with 84 illustrations and 14 tables. Baltimore: Williams and Wilkins, 1952. $6.50.

This synopsis, written for students, covers the whole field of neurology, including neuroanatomy. It requires previous study with a textbook. There is a comprehensive index. The book, which was printed in Great Britain, is well published.

Essentials in Diseases of the Chest for Students and Practitioners. By Philip Ellman, M.D., F.R.C.P., consultant physician in diseases of the chest to the North-East Metropolitan Regional Hospital Board at East Ham Chest Clinic, Harts Sanatorium and Plaistow Hospital Chest Unit, London, and consultant physician, St. Stephen's Hospital (Rheumatism Unit), London, and Dorking General and Leatherhead Hospitals. With a foreword by Sir Robert A. Young, C.B.E., M.D., F.R.C.P., consulting physician to King Edward VII Sanatorium, Midhurst, and vice-chairman of the Council of the National Association for the Prevention of Tuberculosis. 8°, cloth, 400 pp., with 193 illustrations. New York: Oxford University Press, 1952. $6.50.

In this special book the author discusses the diseases of the respiratory organs. Special consideration is given to pulmonary tuberculosis and its treatment. The material is based on personal observations. The illustrations are excellent. The printing was done in Great Britain with a good type. The publishing is good.

NOTICES

EXAMINATION FOR MEDICAL OFFICER

The United States Civil Service Commission has announced a new examination for medical officers for filling positions in various specialized fields of medicine, with salaries ranging from $5,940 to $10,800 a year. The positions are principally in the Bureau of Indian Affairs, located on reservations west of the Mississippi River and in Alaska. A few positions may be filled in the Fish and Wildlife Service. Applicants must be fully qualified as doctors of medicine, and for most positions must be currently licensed to practice medicine and surgery in a state or territory of the United States. Appropriate experience is required.

Further information and application forms may be obtained from the United States Civil Service Commission, Washington 25, D. C., or from most first-class and second-class post offices. Applications will be accepted until further notice by the Board of United States Civil Service Examiners, Bureau of Indian Affairs, Department of the Interior, Washington 25, D. C.

TUFTS MEDICAL ALUMNI ASSOCIATION

The Annual Dinner Meeting of Tufts Medical Alumni Association will be held at the Somerset Hotel, Boston, on April 15, at 6:30 p.m.

The guest speaker is to be Dr. Louis H. Bauer, president of the American Medical Association, who will speak on the subject "The American Medical Association and the Problems Facing Medicine." Acting President, Dr. Nils Wessell, of Tufts College, will speak on the subject "A Plea for Research in Medical Education." Dr. Joseph M. Hayman, Jr., dean of Tufts College Medical School, will make general comments. Dr. Christopher Duncan, associate surgeon-in-chief, Free Hospital for Women in Brookline, will speak on the subject "Reflections of the 25 Year Class."

Dr. James F. Collins, associate medical director of the Boston City Hospital, will preside. Dr. John Cauley, Health Commissioner of Boston, is chairman. Dr. Harry Blotner is secretary, and William E. Browne is president of the committee.

The twenty-five-year class (1928) will hold its reunion on April 14 and 15.

Before the dinner, there will be Open House at the Medical School from 10:30 a.m. to 4:00 p.m.

POSTGRADUATE COURSE IN OBSTETRICS AND PEDIATRICS

As previously announced, the Postgraduate Course in Obstetrics and Pediatrics conducted by the Boston Lying-in Hospital and the Children's Hospital, with the co-operation of the Massachusetts Department of Public Health, will be held April 16–18.

Program

Thursday, April 16 (Boston Lying-in Hospital auditorium)		
9:00 a.m.	Registration (auditorium).	
9:30 a.m.	Dr. B. Alexander.	Present Concepts of Clotting.
10:00 a.m.	Dr. D. J. Mullane.	Thrombosis.
10:45 a.m.	Dr. D. E. Reid.	Amniotic-Fluid Infusion Syndrome.
11:30 a.m.	Dr. C. Smith.	Hemorrhagic Disease of Newborn.
12:00 m.	Dr. K. Benirschke.	Clinicopathological Conference.
1:00 p.m.	Luncheon (cafeteria).	
2:00 p.m.	Dr. B. Hershenson.	Obstetric Anesthesia.
2:30 p.m.	Dr. R. Adams.	Neurologic Complications of Anesthesia.
3:00 p.m.	Dr. J. Strieder.	Respiratory Complications of Anesthesia.
3:45 p.m.	Dr. M. Pendleton.	Neonatal Respiratory Complications.
4:15 p.m.	Dr. H. Leighton.	Modern Obstetric Blood Bank.
Friday, April 17 (Boston Lying-in Hospital auditorium)		
7:30 a.m.	Drs. Reid, Goethals, Eades, Abramson and Bristol.	Obstetric Rounds (analgesia, anesthesia and delivery technics).
	Drs. Clifford, Smith, Pendleton and Allers.	Nursery Rounds.
10:00 a.m.	Drs. M. F. Eades, T. Goethals and C. Hinman.	Indications and Contraindications of Cesarean Section — Cephalopelvic Disproportion — Abnormal Presentation — Bleeding.
10:45 a.m.	Dr. D. E. Reid.	Conduct of Normal Labor and Delivery.
11:30 a.m.	Dr. K. Benirschke.	Clinicopathological Conference.
12:30 p.m.	Forum — questions and answers.	
1:00 p.m.	Luncheon (cafeteria).	
Friday, April 17 (Main Amphitheater, Children's Hospital)		
2:00 p.m.	Dr. L. K. Diamond.	Blood Dyscrasias of Infancy and Childhood.
2:30 p.m.	Dr. F. Allen.	Management of Erythroblastosis Fetalis.
3:00 p.m.	Question period.	
3:30 p.m.	Dr. W. Berenberg.	Differential Diagnosis of Acute Poliomyelitis.
4:00 p.m.	Dr. T. Weller.	Identification of the Virus of Acute Poliomyelitis.

4:30 p.m.	Dr. C. A. Janeway.	Use and Availability of Gamma Globulin in Control of Infectious Diseases.
5:00 p.m.	Question period.	

Saturday, April 18 (Main Amphitheater, Children's Hospital)

9:00 a.m.	Dr. D. Davidson.	Drugs of Choice in the Treatment of Recurrent Seizures.
9:30 a.m.	Dr. E. B. Neuhauser.	Recognition of Congenital Anomalies of Gastrointestinal Tract by Roentgenologic Examination.
10:00 a.m.	Question period.	
10:30 a.m.	Dr. S. Gellis.	Jaundice and Hepatitis in Infancy and Childhood.
11:30 a.m.	Question period (all participants in program present).	

NEW YORK SOCIETY FOR CIRCULATORY DISEASES AND NEW YORK CARDIOLOGICAL SOCIETY

A joint meeting of the New York Society for Circulatory Diseases and the New York Cardiological Society will be held in Room 440, New York Academy of Medicine, on Tuesday, April 14, at 8:30 p.m. The program, which will consist of a symposium on the "Treatment of Circulatory Disturbances of the Extremities," is as follows:

Arterial Insufficiency. Saul S. Samuels, M.D., director of angiology, Brooklyn Hospital for the Aged.

Venous Obstruction and Insufficiency. Jere W. Lord, Jr., M.D., associate professor of clinical surgery, New York University Post-Graduate Medical School.

Chronic Lymphedema. Jules D. Gordon, M.D., attending surgeon, Beth David Hospital.

Programs may be obtained from the Secretary, Gabriel F. Greco, M.D., 114-08 Linden Boulevard, Ozone Park 16, New York.

SOCIETY OF AMERICAN BACTERIOLOGISTS

The spring meeting of the Northeast Branch, Society of American Bacteriologists, will be held at the Massachusetts General Hospital, on Friday, March 27. The afternoon session, at 4 p.m., will be devoted to brief research papers. After the dinner, Dr. David Weinman, of the Department of Microbiology, Yale University School of Medicine, will speak on the subject "Toxoplasmosis." All are welcome. Dinner reservations may be made with Dr. Genevieve Young, Boston University School of Medicine, 675 Commonwealth Avenue, Boston.

AERO MEDICAL ASSOCIATION

The twenty-third annual meeting of the Aero Medical Association will be held at the Biltmore Hotel, Los Angeles, May 11, 12 and 13. The secretary is Thomas H. Sutherland, M.D., P.O. Box 26, Marion, Ohio.

FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY

The annual meeting of the Federation of American Societies for Experimental Biology will be held at the Conrad Hilton Hotel, Chicago, April 6-10. Scientific sessions, including reports of new research, will be presented and discussed. The Federation includes the American Physiological Society, American Society of Biological Chemists, American Society for Pharmacology and Experimental Therapeutics, American Society for Experimental Pathology, American Institute of Nutrition and American Association of Immunologists.

SOCIETY MEETINGS AND CONFERENCES

MARCH 23. Postgraduate Course in General Medicine. Cushing Veterans Administration Hospital, Framingham. Page 697, issue of October 30.

MARCH 23-30. Springfield Hospital Educational Program. Page 396, issue of February 26.

MARCH 23-27. Consultation Clinics for Crippled Children in Massachusetts. Page 353, issue of February 19.

MARCH 23-MAY 4. Massachusetts Department of Mental Health. Postgraduate Seminar in Neurology and Psychiatry. Page 540, issue of October 2.

MARCH 25. Cutter Lecture. Page 307, issue of February 12.

MARCH 25. Graduate Club of Boston, Phi Delta Epsilon Medical Fraternity. Page 307, issue of February 12.

MARCH 25-APRIL 8. Postgraduate Medical Institute. Boston. Page 452, issue of September 18.

MARCH 27. Combined Anesthesia Teaching Conference of Boston. Page 210, issue of January 29.

MARCH 27. Society of American Bacteriologists. Notice above.

MARCH 30. Children's Cancer Research Foundation. Page 480, issue of March 12.

APRIL 1. Postgraduate Medical Institute Course in General Medicine. Burbank Hospital, Fitchburg. Page 1049, issue of December 25.

APRIL 4. Problems in Hematology. Dr. William B. Castle and Dr. Frank Gardner. Mount Auburn Hospital, Cambridge. 10:05 a.m.

APRIL 6-10. Federation of American Societies for Experimental Biology. Notice above.

APRIL 6 AND 20. Hartford Medical Society. Page 42, issue of January 1.

APRIL 1-27. Consultation Clinics for Crippled Children in Massachusetts. Page 523.

APRIL 10. New England Society of Anesthesiologists. Page 395, issue of February 26.

APRIL 10-12. American Association of the History of Medicine. Page 308, issue of February 12.

APRIL 14. New York Society for Circulatory Diseases and New York Cardiological Society. Notice above.

APRIL 15. Annual Tufts Medical Alumni Association. Page 525.

APRIL 15. Massachusetts Academy of General Practice. Page 480, issue of March 12.

APRIL 16-18. Postgraduate Course in Obstetrics and Pediatrics. Page 525.

APRIL 19-24. National Industrial Health Conference. Page 308, issue of February 12.

APRIL 25. Alumni Association of the State University College of Medicine at New York City. Page 396, issue of February 26.

APRIL 25. Graduate Club of Boston. Phi Delta Epsilon Medical Fraternity. Page 307, issue of February 12.

APRIL 29 AND OCTOBER 28. New England Obstetrical and Gynecological Society. Page 868, issue of November 27.

MAY 7-9. American Goiter Association. Page 480, issue of March 12.

MAY 11-13. Aero Medical Association. Notice above.

MAY 19-21. Massachusetts Medical Society. Hotel Statler, Boston.

MAY 25-31. First World Congress on Fertility and Sterility. Page 1001, issue of December 18.

JUNE 7-9. American College of Cardiology. Page 395, issue of February 26.

JUNE 28-JULY 2. American Society of X-Ray Technicians. Page 480, issue of March 12.

DISTRICT MEDICAL SOCIETIES

ESSEX NORTH

MAY 13. Andover Country Club, Shawsheen.

MIDDLESEX WEST

MARCH 23. Postgraduate Course in General Medicine, Cushing Veterans Administration Hospital, Framingham.

NORFOLK

MARCH 24.

WORCESTER

MAY 6. Annual Meeting. Sheraton Hotel. Dr. Louis H. Bauer, President, American Medical Association.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, MARCH 26

THURSDAY, MARCH 26

*8:30-10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.

9:00-10:00 a.m. Grand Rounds. Russell Room, House of the Good Samaritan.

9:00-10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

*11:00 a.m.-12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.

*11:00 a.m.-12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

*12:00 m.-1:00 p.m. Cases of Probable Suicide in Young Persons without Obvious Motivation. Dr. A. Warren Stearns. Stearns Auditorium. New England Center Hospital.

12:30-1:30 p.m. Lecture in Pathology. Joslin Auditorium, New England Deaconess Hospital.

*5:00-6.00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

FRIDAY, MARCH 27

8:00-9:00 a.m. Diabetes Clinic by members of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.

*10:00 a.m.-1:00 p.m. Medical and Surgical Grand Rounds. Dr. George W. Thorn and Dr. Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.

*10:30-11:15 a.m. Diabetes Lecture. Dr. Elliott Joslin. New England Deaconess Hospital.

*10:30 a.m.-1:30 p.m. Combined Medical and Surgical Rounds, Stearns Auditorium, New England Center Hospital.

(Notices concluded on page xvii)

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MEDICAL SECRETARY, registered nurse, with experience, desires position in Back Bay surgeon's office. Address A178, *New Eng. J. Med.* 5-tf

WANTED — General practitioners to take day and night calls in vicinity of Cambridge. Address A179, *New Eng. J. Med.* 5-12t

ANESTHESIOLOGY — Approved residency at Eastern Maine General Hospital, Bangor, Maine; training all phases of modern anesthesiology; 1 and 2-year appointments available July 1, 1953. Write Clement S. Dwyer, M.D., Department of Anesthesiology. B223-9-4t

FOR SALE — Newtonville, 18-room house, 5 bathrooms, insulated, new air conditioner (heater). House built for doctor and occupied by him for 30 years. Large lot. Heated garage. Address A185, *New Eng. J. Med.* 12-1t

PEDIATRICIAN — 31, board eligible, priority IV, family, now resident at large eastern pediatric hospital, desires practice in moderate-sized community. Address A207, *New Eng. J. Med.* 12-2t

MEDICAL SECRETARY, Colby Junior College graduate, experienced, desires position, Metropolitan Boston or suburbs, preferably physician's office. Will consider other positions. Address A208, *New Eng. J. Med.* 12-2t

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LOCUM TENENS for general practice, 20 miles south of Boston for May, June and July, 1953, or any part thereof. Terms arranged. Office in home. Housekeeper and nurse to assist. Address A174, *New Eng. J. Med.* 4-tf

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Psychiatrist for Private Mental Hospital near Boston. Salary by arrangement. Address A209, *New Eng. J. Med.* 12-6t

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WANTED — Well-trained medical man in tuberculosis in 90-bed sanatorium, located within 30 miles of Boston. Must be experienced in pneumothorax and pneumoperitoneum as well as other modern methods of treatment. Present physician is being called into military service July 1, 1953. Salary $3815 per year plus full maintenance. Address A210, *New Eng. J. Med.* 12-3t

SURGEON, 31, board eligible, desires New England location. Community under 50,000. Would consider group, association or private practice. Address A202, *New Eng. J. Med.* 10-3t

Young physician, with experience in INTERNAL MEDICINE and 3 years' research and teaching in medical sciences, desires part to full-time practice with internist in Greater Boston area. Address A211, *New Eng. J. Med.* 12-2t

FOR SALE — 9-room house and doctor's office with reception room. Occupied by physician for past 25 years. Centrally located in Hyde Park, Mass. Telephone HY 3-0171-R. B234-12-1t

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FOR SALE — Successful general practice in town of 11,000, home and office combination in best location of town. Equipment optional. Will introduce. Address A206, *New Eng. J. Med.* 11-3t

FOR SALE — General practice, corner Columbia Road and Dorchester Avenue, Dorchester. Complete office equipment. Best offer accepted. Address A197, *New Eng. J. Med.* 9-tf

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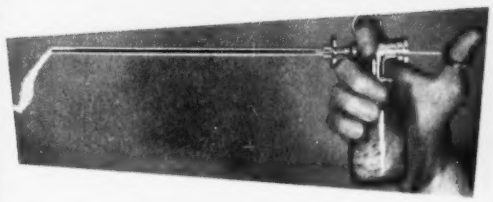

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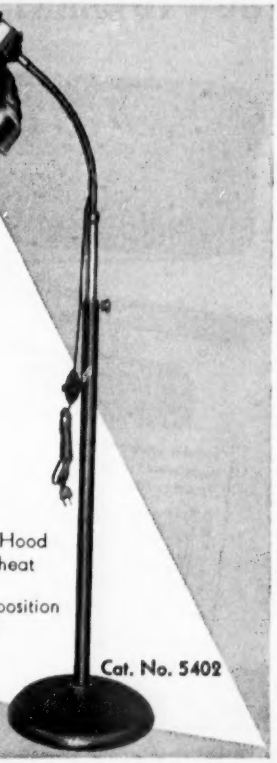

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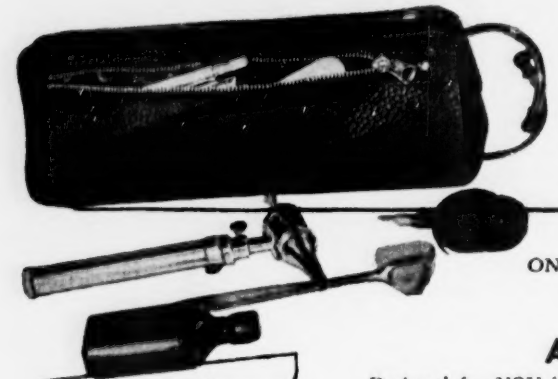

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NOTICES (*Concluded from page 526*)

*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.

*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.

*2:00–3:00 p.m. Pulmonary Conference. Drs. Kane, Etsten, Woods and others. Stearns Auditorium, New England Center Hospital.

*4:00 p.m. Society of American Bacteriologists Massachusetts General Hospital.

*4:00–6:00 p.m. X-ray Conference. Drs. Sosman and Fleischner. Stearns Auditorium, New England Center Hospital.

*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

*7:00–9:00 p.m. Combined Anesthesia Teaching Conference of Boston. Amphitheater, Evans Memorial, Massachusetts Memorial Hospitals, Eighth Floor, 65 East Newton Street.

SATURDAY, MARCH 28

8:00–9:00 a.m. Lahey Clinic Medical Conference. Dr. Donald P. Cyr. Joslin Auditorium, New England Deaconess Hospital.

*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.

*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.

*11:00 a.m.–12:00 m. Blood Clinic. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, MARCH 30

8:00–9:00 a.m. Combined Medical and Surgical Rounds for Diabetic Surgery Cases. New England Deaconess Hospital.

*8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.

*12:00 m.–1:00 p.m. Medical Conference. Drs. George W. Mitchell and S. Charles Kasdon. Stearns Auditorium, New England Center Hospital.

*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

*2:00–8:30 p.m. Postgraduate Seminar in Neurology and Psychiatry. Metropolitan State Hospital, Waltham.

5:15 p.m. Staff Meeting. Harris Hall, New England Deaconess Hospital.

*7:00–9:00 p.m. Anesthesia Teaching Conference. Stearns Auditorium, New England Center Hospital.

8:15 p.m. Massachusetts Society for Research in Psychiatry. Ring Sanatorium, Arlington Heights.

TUESDAY, MARCH 31

*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.

11:00 a.m.–12:00 m. Regular Grand Rounds of the Pediatric Department. Dowling Amphitheater, Boston City Hospital.

*12:00 m.–1:00 p.m. Medical Conference. Dr. Ralph Levin. Stearns Auditorium, New England Center Hospital.

*12:00 m.–1:00 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

*12:15–1:15 p.m. X-ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.

5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.

*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.

WEDNESDAY, APRIL 1

*12:00 m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.

*12:00 m.–1:00 p.m. Clinicopathological Conference. (Children's Medical Center.) Jimmy Fund Building, 25 Binney Street.

12:30 p.m. Weekly Pathological Meeting. Joslin Amphitheater, New England Deaconess Hospital.

12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.

*4:00 p.m. Thoracic Conference. Held by Overholt Clinic. Harris Hall, New England Deaconess Hospital.

*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.

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1. Frost, L. H., and Jackson, R. L.: J. Pediat. 39: 585-592, 1951.

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